

UNIVERSITY OF BIRMINGHAM

CONTROLLED OVARIAN STIMULATION PROTOCOLS, SERUM LUTEAL PROGESTERONE AND IMMUNOMODULATORS IN WOMEN UNDERGOING ASSISTED CONCEPTION

by

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Abstract

Infertility affects an estimated 48.5 million couples globally. Approximately 5-10% of couples with infertility require assisted reproductive technology (ART) to conceive a pregnancy. Since the birth of Louise Brown in 1978, ART procedures have evolved to include complex ovarian stimulation protocols, in vitro treatment with cryopreservation of gametes or embryos, and adjuvant interventions aimed at improving reproductive outcomes. However, despite these advances and the growing number of ART cycles performed worldwide, the rates of live birth resulting from assisted conception remain relatively low.

The success of ART depends on a complex biochemical dialogue between the implanting embryo and the endometrium. Factors such as ploidy status and metabolic competency affect embryo quality, while endometrial receptivity involves developing a tolerant immuno-endocrine milieu to the attaching embryo.

This thesis investigates optimisation strategies to improve ART success. I use a range of methodologies, including systematic reviews of randomised controlled trials, network meta-analysis and prospective observational data, to propose tangible ways to enhance treatment effectiveness and improve safety at various stages of assisted conception.

The main findings are:

1. Controlled ovarian stimulation (COS) protocols vary in their effectiveness and safety. The Cochrane network meta-analysis in this thesis confidently demonstrates that short gonadotrophin-releasing hormone (GnRH) antagonist protocols reduce ovarian hyperstimulation syndrome rates in women with predicted normal and

high response compared to long GnRH agonist protocols. Notably, the data did not confidently identify a difference in live birth rates between these two main COS protocols.

2. Women with low serum progesterone (<10 ng/ml) undergoing frozen embryo transfer (FET) cycles experience fewer live births and an increased risk of miscarriage compared to women whose serum progesterone level is ≥10 ng/ml.
3. The route of progesterone administration in FET cycles affects the relationship between serum progesterone and the probability of live birth. Women having natural cycle FET (endogenous progesterone) or vaginal progesterone supplementation exhibit a near-linear association between serum progesterone and the adjusted mean probability of live birth, whereas this relationship is non-linear for those receiving exclusively subcutaneous progesterone supplementation for luteal phase support. Combined therapy with vaginal and subcutaneous progesterone may synergistically ensure stable live birth rates irrespective of serum progesterone levels.
4. The evidence for immunological therapies during the luteal phase to improve the rate of live birth in ART is mostly of low or very low certainty, although some drugs may lead to improved outcomes in selected women.

Dedication

I dedicate this thesis to my mother, Lourdes, for showing me the power of hard work and grit, and to my father, António, whose kindness and sense of humour have always made hard times easier. I would have never come this far without your example and unwavering support.

I also dedicate this to Joe, for his love, patience, and ability to remind me of what truly matters in life from time to time. And for the dad jokes, too.

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LIST OF ABBREVIATIONS (MAIN THESIS BODY)

AMH – anti-Müllerian hormone

ART – assisted reproductive technology

CHO – Chinese hamster ovary

COS – controlled ovarian stimulation

DNA – deoxyribonucleic acid

ESHRE – European Society of Human Reproduction and Embryology

FET – frozen embryo transfer

FSH – follicle-stimulating hormone

G-CSF – granulocyte-colony stimulating factor

GHD – gestational hypertensive disorders

GnRH – gonadotrophin-releasing hormone

hCG – human chorionic gonadotrophin

hMG – human menopausal gonadotrophin

HRT-FET – hormone replacement therapy frozen embryo transfer

ICSI – intracytoplasmic sperm injection

IU – international units

IVF – in vitro fertilisation

IVIG – intravenous immunoglobulin

LH – luteinising hormone

LPD – luteal phase defect

LPS – luteal phase support

NC-FET – natural cycle frozen embryo transfer

NHS – National Health Service

NMA – network meta-analysis

OHSS – ovarian hyperstimulation syndrome

OI – ovulation induction

PGT-A – preimplantation genetic testing for aneuploidies

PMBCs – peripheral blood mononuclear cells

rhCG – recombinant human

r-hLIF – recombinant human leukaemia inhibitory factor

rLH – recombinant luteinising hormone

TVUS – transvaginal ultrasound

uFSH – urinary follicle-recombinant hormone

WHO – World Health Organization

CHAPTER 1: THESIS INTRODUCTION

1.1. Epidemiology of infertility

The World Health Organization defines infertility as the inability to achieve pregnancy despite regular unprotected sexual intercourse for twelve or more months (1). Infertility affects approximately 1 in 6 reproductive-aged couples, amounting to an estimated 186 million people living with this condition worldwide (1-3). There are many known causes of infertility. These include female disorders (e.g., ovulatory problems, fallopian tube damage, endometriosis or uterine abnormalities), male disorders (e.g., testicular failure, post-testicular blockage), or a combination of female and male factors. Yet, 1 in 4 cases of infertility remains unexplained (2).

In recent decades, assisted reproductive technology (ART), whereby human oocytes, sperm and embryos are handled outside the body to achieve a pregnancy, has significantly improved pregnancy outcomes for couples living with infertility (4). Worldwide, more than eight million babies have been born from in vitro fertilisation (IVF) since its inception in 1978, and over two million treatment cycles are performed globally every year (5).

1.2. Overview of assisted reproductive technology

Assisted reproductive technology involves a series of steps requiring meticulous planning by clinicians and embryologists. Firstly, women receive drugs to stimulate the growth of several ovarian follicles instead of relying on the development of one dominant follicle that usually occurs in a natural menstrual cycle. Secondly, additional drugs (gonadotrophin-releasing hormone [GnRH] analogues or progestogens) are concomitantly administered

with stimulation agents to suppress the pituitary function, thus preventing premature luteinisation. The process of administering exogenous hormones to promote the concurrent development of several ovarian follicles while the pituitary gland is suppressed is termed “controlled ovarian stimulation” (COS) (6-9).

Women undergoing COS are closely monitored with regular transvaginal ultrasound (TVUS) to assess the growth of follicles. Once one or more follicles reach ≥17 mm of maximum diameter, oocyte maturation is triggered by administering drugs with similar biochemical structure and activity to luteinising hormone (LH) (10, 11). Human chorionic gonadotrophin (hCG) has historically been the drug of choice for triggering ovulation, owing to improved half-life and potency compared to LH (12, 13). Women undergo oocyte retrieval approximately 34-38 hours after ovulation trigger, under TVUS guidance (8). In vitro insemination ensues by either incubating an oocyte with a concentrated semen sample (conventional IVF) or performing intracytoplasmic sperm injection (ICSI).

Following fertilisation, embryos are incubated in special culture media and transferred into the woman’s uterus on days 2-6 of embryo development. The timing of embryo transfer remains a topic of debate. However, recent evidence suggests that transfer at the blastocyst stage (days 5 or 6) results in improved live birth rates in comparison to embryo transfer at the cleavage stage (days 2 to 4 of development) (14).

Embryos that are not transferred and survive the culturing process can be cryopreserved and used in future treatment cycles, thus circumventing the need for additional rounds of COS. Frozen-thawed embryo transfer (FET) cycles exhibit similar effectiveness to fresh

transfer cycles (15, 16). Moreover, FET cycles are simpler and less expensive to undertake (17).

Lastly, different hormones (progesterone, oestradiol, hCG or a combination of hormones) may be used to support embryo development in the first few weeks of pregnancy, until the placenta takes over to synthesise these hormones endogenously. This is termed "luteal phase support" (18).

1.3. Principles of controlled ovarian stimulation

Controlled ovarian stimulation is a complex process. It requires the administration of drugs that stimulate the ovaries to develop more than one follicle (usually oral ovulation induction [OI] agents, gonadotrophins, or a combination of both types of drugs), in addition to medications that suppress the pituitary gland to prevent premature luteinisation and ovulation (usually GnRH analogues or progestogens) (19).

1.3.1. Oral agents for ovarian stimulation

Clomifene citrate

Clomifene citrate has been used in ovulation induction since the early 1960s (20). It is a selective oestrogen receptor modulator exhibiting agonist or antagonist activity depending on endogenous oestrogen levels. Clomifene exerts antagonistic effects upon oestrogen receptors mainly in the hypothalamus and, to a lesser extent, the pituitary gland (21). Its central blockage of oestrogen receptors disrupts the negative feedback loop exerted by circulating oestradiol levels, resulting in increased FSH secretion by the pituitary. Rising circulating FSH levels, in turn, act on the granulosa cells in the ovary and promote follicle growth and a rise in oestradiol levels (22).

Clomifene is administered at a daily dose of 50-150 mg for five days in the early follicular phase (from days 2 to 6, or days 3 to 7), with or without gonadotrophin injections (23, 24). Importantly, clomifene has been associated with thinning of the endometrium, raising concerns about receptiveness to the implanting embryo (25, 26).

Letrozole

Letrozole inhibits the enzyme aromatase, which is responsible for converting androgens into oestrogens in the granulosa cells of ovarian follicles. This reduces the levels of circulating estradiol, largely eliminating its negative feedback upon the pituitary gland, whose secretion of FSH increases (27). Like clomifene citrate, letrozole is usually administered for five days at the beginning of the menstrual cycle, in doses ranging between 2.5 and 7.5 mg once daily, titrated according to response (28, 29). The side effects of letrozole include hot flushes and gastrointestinal discomfort, although they are rarely severe (30).

1.3.2. Gonadotrophins for ovarian stimulation

In COS for IVF, exogenous gonadotrophins are almost universally used to induce multifollicular growth, although some authors suggest that oral agents may have a role in women with predicted low response, either alone or in combination with gonadotrophins (24, 28, 29). Various types of gonadotrophins exist, differing in source, molecular composition, purity and administration route.

Urinary gonadotrophins

Urinary gonadotrophins are derived from the urine of postmenopausal women, who excrete high levels of FSH and LH, and pregnant women, whose urine contains high hCG levels (31). These drugs have been commercially available since the 1960s and were initially

used exclusively for ovulation induction in women with anovulation. A decade later, the advent of IVF brought about the routine use of gonadotrophins for ovarian stimulation before oocyte retrieval. Because these gonadotrophins were initially extracted from the urine of postmenopausal women, the combination of FSH and LH was called human menopausal gonadotrophin (hMG) (32). Such preparations contained both FSH and LH in a 1:1 ratio, yet the presence of other urinary protein compounds reduced their purity. Thus, the first generation of hMG drugs featured high inter-batch variation and substantial immunogenicity requiring intramuscular administration (33). It is also important to note that the need to obtain urine from human volunteers renders hMG a potentially finite resource.

As extraction methods improved, pharmaceutical companies developed highly purified hMG preparations, with the first product introduced in Europe in 2000 (34). Although the ratio of FSH to LH remained 1:1, these refined formulations contained a reduced amount of contaminants. They were, therefore, suitable for subcutaneous administration, lowering the risk of allergic reactions and increasing patient tolerability to daily injections (31, 33).

Because of evidence demonstrating the predominant role of FSH upon initial follicle recruitment and development, as well as concerns about the potentially harmful effect of LH upon endometrial receptivity, preparations containing purified urinary FSH (uFSH) were also introduced in the 1980s (31). Historically these included varying degrees of LH activity, whereas today, highly purified uFSH drugs hold fewer than 0.1 international units (IU) of LH per 1 IU of FSH (33). In addition, urinary FSH preparations are usually more acidic than recombinant forms due to differences in glycosylation patterns (31).

Recombinant gonadotrophins

In the 1990s, the massification of recombinant DNA technology led to the development of synthetic gonadotrophin formulations, whose manufacturing was possible in industrial amounts using Chinese hamster ovary (CHO) cells. Pharmaceutical companies have since released many recombinant forms, including rFSH, rLH and rhCG. These offer improved accessibility, large-scale manufacturing, minimal batch-to-batch variation and low immunogenicity. They are also administered subcutaneously, resulting in less pain and fewer adverse reactions compared with some intramuscular urinary preparations (31, 33).

Multiple FSH preparations exist worldwide, but not all FSH drugs are identical. This is because there are many FSH isoforms, which despite featuring a similar core structure, possess varying biochemical properties owing to different post-translational modifications within the FSH molecules, including glycosylation and the addition of sialic acid residues (35). The first rFSH formulation, introduced in 1995, was named follitropin alpha, and there have since been various additional preparations, including follitropin beta and follitropin delta, whose biochemical structure varies slightly (36). Follitropin alpha and beta are synthesised in CHO cells, while follitropin delta is unique because its manufacturing requires human fetal retinal cells (37). Additional biochemical modifications affect the pharmacokinetics of rFSH preparations. For example, corifollitropin alpha is a type of rFSH whose long half-life allows the effect of a single injection to last for seven days, thus requiring much fewer injections for stimulation and improving patient tolerability to treatment (31, 33).

1.3.3. Gonadotrophin-releasing hormone and analogue drugs

Gonadotrophin-releasing hormone is a tropic peptide hormone synthesised and released from hypothalamic GnRH neurons in a pulsatile fashion. Once produced, GnRH is secreted into the portal blood vessels and carried to the pituitary gland, where it acts on G-coupled receptors on the apical surface of anterior pituitary cells (38, 39). The binding of GnRH to these receptors induces the release of gonadotrophins (FSH, LH), whose synthesis otherwise occurs in periods of absent GnRH binding. Secreted FSH and LH will then regulate the follicular and luteal phases of the menstrual cycle (40).

Gonadotrophin-releasing hormone analogues, including agonists and antagonists, are structurally similar to endogenous GnRH.

GnRH agonists

Gonadotrophin-releasing hormone agonists were the first drugs used for pituitary suppression in COS before IVF. Like endogenous GnRH, GnRH agonists are decapeptide molecules. However, changes in the amino acid sequence (specifically positions 6 and 10) result in improved affinity towards GnRH receptors in the pituitary and a prolonged half-life compared to the natural GnRH hormone (41). Once administered, GnRH agonists exert a transient flare effect, increasing FSH secretion. Yet, continued agonist administration desensitises the GnRH receptors, resulting in pituitary downregulation after 10-14 days (42). This prevents a premature endogenous LH surge, thus allowing assisted conception practitioners to appropriately time ovulation triggering and oocyte retrieval.

Examples of GnRH agonist drugs include buserelin, triptorelin, leuprorelin, nafarelin, deslorelin and goserelin. They vary according to route (subcutaneous, intramuscular,

nasal), dose, and frequency of administration (depot injection, daily injection or nasal administration several times a day) (43). Prolonged administration of GnRH agonists may result in a profound hypoestrogenic state, which often manifests through menopause-like symptoms including hot flushes, lethargy, low libido and vaginal dryness. These symptoms may persist after discontinuation of the GnRH agonist drug but usually resolve within 2-4 weeks (42, 44).

GnRH antagonists

The use of GnRH antagonists is akin to performing chemical hypophysectomy. Antagonist molecules contain ten amino acids, of which positions 1, 2, 3, 6 and 10 differ from those of endogenous GnRH (45, 46). They exhibit medium affinity (i.e., higher than that of natural GnRH, but lower than that of GnRH agonists) towards GnRH receptors and have an immediate onset of action (47).

Examples of GnRH antagonists include cetrorelix and ganirelix. Because they are administered for a short time and only after the onset of ovarian stimulation with gonadotrophins, GnRH antagonists rarely induce pituitary hormone withdrawal symptoms and are well tolerated. In addition, once these drugs are discontinued, pituitary function resumes as normal (48).

1.4. Controlled ovarian stimulation protocols

Historically, stimulation protocols involved using gonadotrophin drugs in a natural menstrual cycle, followed by an ovulation trigger injection and oocyte retrieval 36-40 hours later. Unfortunately, premature ovulation was common in such protocols, resulting in high

cancellation rates and failure to collect oocytes (49). In the 1980s, clinicians began using GnRH agonists for pituitary downregulation before ovarian stimulation with gonadotrophins (50). Since then, various protocol variations have been introduced into clinical practice, including administering GnRH antagonists instead of agonist drugs.

1.4.1. Long GnRH agonist protocols

Long agonist protocols involve the administration of GnRH agonists for pituitary downregulation before ovarian stimulation. There are various regimens to achieve downregulation with GnRH agonists. They differ in the type of agonist used and frequency of administration. Further, trials have investigated mid-luteal versus follicular initiation of GnRH agonists (51). Approximately one to two weeks after commencement of the agonist drug, or when patients experience menstrual bleeding, downregulation is usually confirmed by visualising quiescent ovaries (with all follicles measuring <10 mm) and a thin endometrial lining (<4-6 mm) on TVUS (52). Once downregulation has been established, ovarian stimulation begins.

In their latest Ovarian Stimulation guideline, the European Society of Human Reproduction and Embryology (ESHRE) recommends a starting gonadotrophin dose of 150-225 IU (53). Where a dose increase is required because of a low ovarian response during stimulation, the evidence suggests that daily amounts of gonadotrophins beyond 300 IU are unlikely to accrue substantial benefit (53). The total duration of gonadotrophin administration varies according to the pace of follicle growth (usually 1-2 mm per day), with most women requiring 10 to 12 days of stimulation before triggering ovulation (54).

1.4.2. Short GnRH antagonist protocols

Unlike long agonist protocols, where pituitary downregulation precedes the administration of gonadotrophins, in short antagonist protocols women commence exogenous gonadotrophins shortly after menstruation. Gonadotrophin-releasing hormone antagonists are then started to prevent premature ovulation and continued until the time of ovulation trigger (55, 56).

An important benefit of GnRH antagonist protocols is that ovulation trigger may be administered both in the form of hCG or GnRH agonist. In women at high risk of ovarian hyperstimulation syndrome (OHSS, e.g., due to a history of polycystic ovary syndrome or high serum anti-Müllerian hormone [AMH]), a GnRH agonist trigger is preferred, as it temporarily displaces the antagonist drug from the pituitary GnRH receptors, thus inducing an endogenous LH surge required for oocyte maturation (57). While this reduces the risk of OHSS, ovulation triggering with GnRH agonists is also insufficient for adequate luteal phase support in fresh IVF cycles (58). For this reason, ESHRE guidance recommends a freeze-all strategy in women undergoing short antagonist cycles with a GnRH agonist trigger. In long agonist cycles, it is impossible to trigger ovulation using GnRH agonists as this would only further suppress the pituitary. Instead, a reduced hCG dose (usually 5,000 international units) should be considered in women at high risk of OHSS (53).

1.4.3. GnRH agonist flare protocols

The administration of GnRH agonists results in an initial flare effect due to a rise in FSH levels lasting a few days, followed by pituitary suppression due to receptor desensitisation.

In agonist flare protocols, the GnRH agonist is started concurrently with gonadotrophins in the early follicular phase of the cycle, and continued until the day of trigger injection to prevent premature ovulation (59). It has been suggested that low-responding women may benefit from such a protocol because of the flare effect, enhanced synthesis of endogenous FSH and reduced duration of downregulation. However, this may result in the development of fewer oocytes and impair endometrial function (60). Nonetheless, existing meta-analyses have not confidently identified a difference in live birth rates compared with long agonist protocols, which appear to result in a higher oocyte number than agonist flare protocols (42).

1.4.4. GnRH agonist flare ultrashort protocols

In agonist flare ultrashort protocols, GnRH agonists are initiated concomitantly with gonadotrophins and continued for only a few days (usually 3), beyond which women continue gonadotrophin injections only. Authors who support such a protocol defend its flare effect and the absence of subsequent pituitary suppression as strategies to improve oocyte yield (61). However, meta-analysis data have not confidently identified an effectiveness benefit in low-responding women (42).

1.4.5. Progestogens for pituitary suppression

There is growing evidence investigating synthetic progestogens (e.g., medroxyprogesterone, dydrogesterone and norethisterone) to induce pituitary suppression during COS (62). These drugs offer improved convenience by avoiding the need for GnRH analogue injections and rendering IVF cycles cheaper. However, premature

induction of the secretory activity of the endometrium by administering progestogens in the follicular phase inevitably results in embryo-endometrial asynchrony. For this reason, cycles using progestogens for pituitary suppression rely on a “freeze all embryos” strategy, precluding fresh embryo transfer (63).

Figure 1 shows examples of commonly used COS protocols.

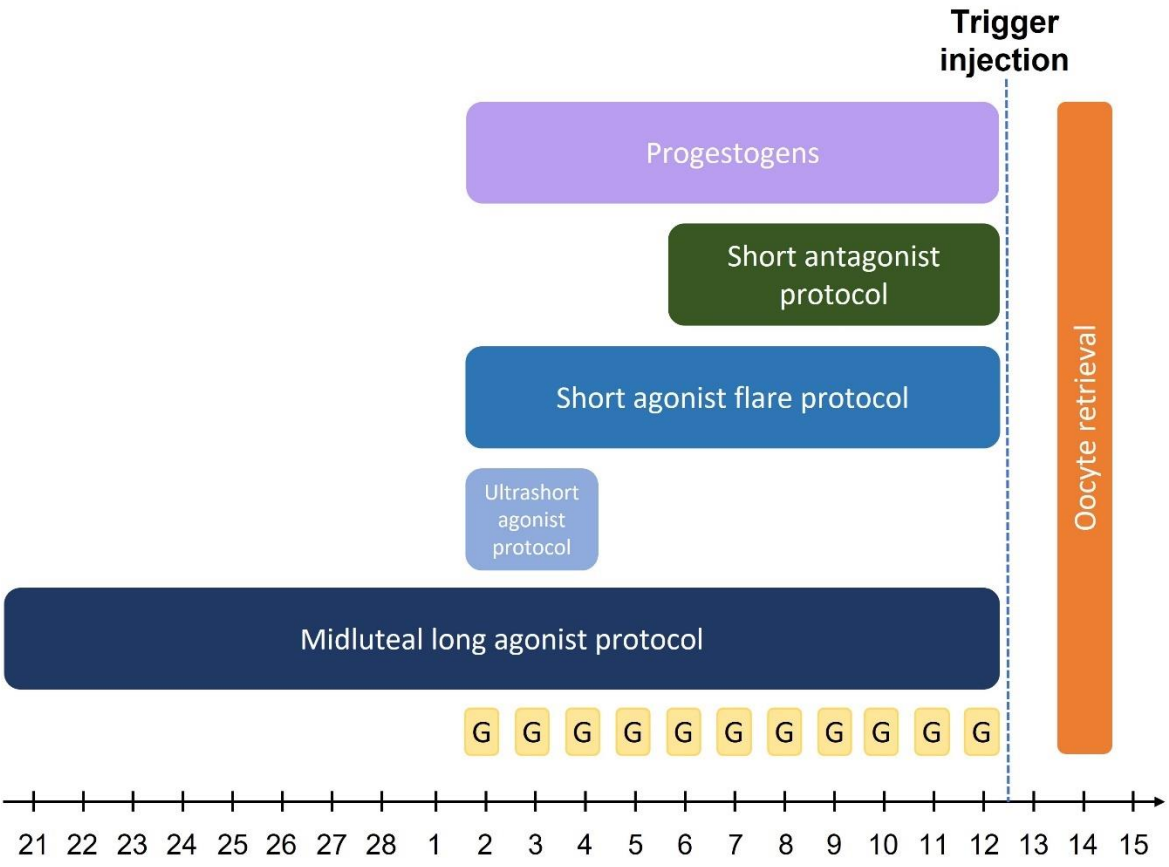


Figure 1. Examples of controlled ovarian stimulation protocols. The horizontal axis represents the days of the menstrual cycle. G = gonadotrophin injection.

1.5. Relative effectiveness and safety of COS protocols

Various systematic reviews and meta-analyses have examined randomised controlled trials (RCTs) investigating head-to-head comparisons between COS protocols (56, 64-69).

However, these reviews are limited by their inability to infer comparisons between interventions that have not been directly studied in RCTs. Network meta-analysis (NMA) differs from standard pairwise comparisons because it uses advanced statistical methodology to infer indirect evidence from existing RCTs investigating a common comparator (Figure 2). Provided that RCTs exist comparing one intervention and any other within one network, it is possible to calculate a weighted estimate using direct and indirect evidence, so that the final effect size corresponds to the network estimate. This allows researchers to compare interventions that may not have been investigated head-to-head in existing RCTs. Further, when enough network evidence exists, it may be possible to use NMA to rank all the interventions in one network according to their effectiveness and safety (70).

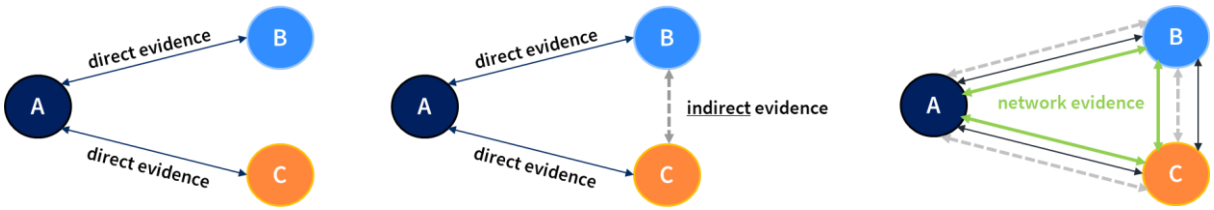


Figure 2. Network meta-analysis. Left: network diagram illustrating direct RCT evidence between treatments A vs B, and A vs C. Middle: inference of the B vs C comparison is possible because of the common comparator (treatment A). Right: the weighing of direct and indirect comparisons between all three treatments results in network estimates and ranking of all three treatments according to effectiveness and safety. RCT, randomised controlled trial.

1.6. The rise in freeze-thaw cycles in assisted conception

According to the Human Fertilisation and Embryology Authority (HFEA), the number of FET cycles in the United Kingdom increased nearly thirteen-fold between 1992 and 2019

(Figure 3). More than 4 in 10 embryo transfers resulted from freeze-thaw cycles in 2019, with FET numbers rising steeply since 2014. In contrast, the number of fresh embryo transfers increased until 2011 but subsequently declined steadily (71).

The increase in FET cycles has been possible because of advances in embryo culture techniques (e.g., extended culture to blastocyst stage) and cryopreservation methods (e.g., vitrification) (72). In turn, FET has improved ART safety by enabling single embryo transfer policies to reduce multiple pregnancy rates and deferral of embryo transfer in women at high risk of OHSS (73). FET has also facilitated progress in applying transcriptomics to time embryo transfer, and preimplantation genetic testing for aneuploidy (PGT-A), although with uncertain effectiveness (74, 75). Nevertheless, the overall success rate of FET cycles remains relatively low, with recent data suggesting an overall live birth rate per embryo transfer of 23% (76). There is a need for high-quality research into interventions to optimise treatment success in FET.

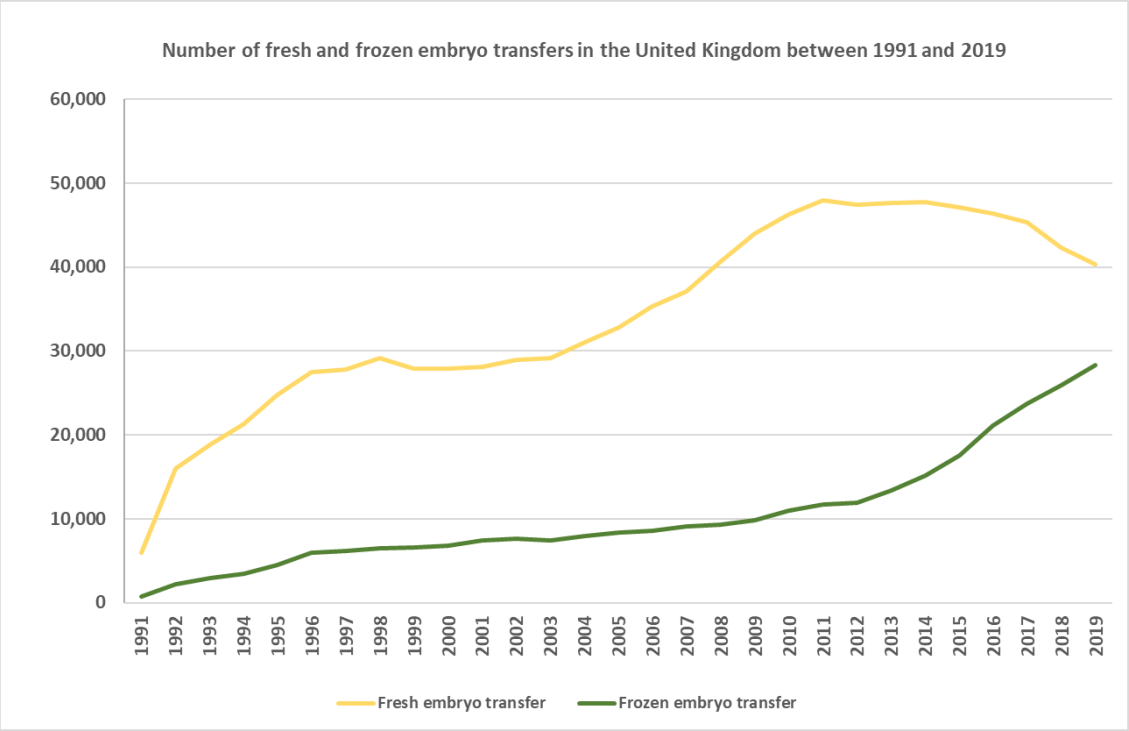


Figure 3. Number of fresh (yellow) and frozen (green) embryo transfers performed in the United Kingdom between 1991 and 2019. Adapted from HFEA (71).

1.7. Progesterone and the luteal phase

Progesterone is a steroid hormone secreted by the corpus luteum after ovulation. In the 1970s, the essential role of progesterone in pregnancy maintenance was demonstrated in studies where removing the corpus luteum from the ovaries of pregnant women led to iatrogenic pregnancy loss in all participants (77, 78). It has since been postulated that even a relative rather than an absolute progesterone deficiency, termed luteal phase defect (LPD), may contribute to pregnancy loss and reduce the chance of live birth in natural conception. However, there has been no consensus on how to define LPD (79). Some suggest that a short luteal phase (≤10 days) may suffice to diagnose LPD, while others have based their diagnosis on low serum progesterone measurements (80).

Fresh IVF cycles have long been known to suffer from a lack of hormonal support during the luteal phase, mainly due to the inhibition of LH secretion (10). The exact mechanism underlying this phenomenon remains unclear. However, existing evidence supports that LPD in fresh cycles may stem from multiple ineffective corpora lutea, whose secretion of progesterone suffices to suppress the pituitary but does not adequately support implantation and pregnancy in its early stages (10). Unsurprisingly, progesterone supplementation in the luteal phase has thus been shown to improve fertility outcomes in women undergoing fresh ART (18). Yet, in a recent prospective study by Thomsen et al. (81), the authors demonstrated that excessive progesterone in the mid-luteal phase (>400 nmol/l) might be just as detrimental to treatment success as insufficient progesterone.

The hypothesis that some patients undergoing FET cycles may also experience LPD has only recently been tested. In a seminal study by Yovich et al. (82), the investigators evaluated the association between serum progesterone levels and FET outcomes after transferring 529 vitrified blastocysts. The evidence demonstrated that progesterone levels within the first quartile (<50 nmol/l) were independently associated with reduced clinical pregnancy and live birth rates, and that progesterone levels above the fourth quartile (>99 nmol/l) also reduced treatment effectiveness (82). Since then, some studies have demonstrated a linear correlation between progesterone levels and pregnancy outcomes, where higher serum progesterone was associated with increased live birth rates and a lower risk of miscarriage (83-86). However, others have suggested an optimum range of serum progesterone above which excessive progesterone nefariously affects treatment outcomes (87).

Mechanistic studies suggest that progesterone exerts various roles in sustaining a pregnancy, both in the uterus and systemically (88). Progesterone induces the secretory activity of the endometrium in early gestation and promotes myometrial quiescence, which is essential to facilitate implantation and prevent preterm labour (89). Systemically, progesterone enables a state of immune tolerance by inducing a shift from a T lymphocyte helper 1 (Th1)-mediated response to a reaction that is mostly Th2-led, and thus more permissive to the semi-allogenic conceptus as it implants upon the maternal decidua (88).

1.8. Other immunomodulatory agents in the luteal phase

Embryo implantation is one of the principal events leading to the establishment of a successful pregnancy. Implantation requires a state of immune tolerance within the maternal endometrium that allows the semi-allogenic embryo to attach to the decidua without being rejected by the mother's immune system (90). This involves a complex biochemical dialogue between the developing embryo and the endometrium, mediated by several key players such as natural killer (NK) and T-cells (91). Absolute implantation failure inevitably precludes ART success, while partial implantation abnormalities may still result in the establishment of a pregnancy. However, it is widely accepted that abnormal implantation exerts a deleterious effect upon pregnancy, resulting in higher risk of complications such as miscarriage and gestational hypertensive disorders (92, 93).

The crucial role of the immune system in allowing embryo attachment has led researchers to hypothesise that immunomodulatory drugs may improve the chance of normal implantation and live birth in women undergoing assisted reproduction technology (ART) treatment. Immunological therapies have therefore been used for decades in assisted

conception, with recent data suggesting that up to 25% of women undergoing IVF choose to pursue treatment with add-on therapies such as aspirin, heparin or corticosteroids (94, 95). Although the mechanisms through which these drugs act vary widely, it is thought that in addition to enhancing blood perfusion within the decidua, immunomodulators may dampen local and systemic inflammation, resulting in improved endometrial receptivity and facilitating implantation (96, 97).

However, despite their use by many ART practitioners, there is no consensus on the effectiveness and safety of immune therapies in women undergoing assisted conception (98, 99).

1.9. Aims and Objectives

This thesis contains a cohesive body of research divided into four manuscripts, of which three have been published (chapters 3, 4 and 5) and one has been accepted for publication (chapter 2). Each paper aims to improve treatment outcomes for women undergoing assisted conception by answering one of the following questions:

A. What is the relative effectiveness and safety of existing COS protocols?
B. What is the existing evidence on the association between serum progesterone levels and FET outcomes?
C. What is the effect of the route of progesterone administration on the association between serum progesterone levels and FET outcomes?
D. What is the current evidence on the effectiveness of immune therapies administered to women with subfertility and/or undergoing assisted conception?

1.10. Summary of thesis

Table 1. *Summary of thesis and structured questions for each thesis chapter.*

Chapter number	Population	Intervention	Comparison	Outcome(s)	Research design	Manuscript status
A. What is the relative effectiveness and safety of existing COS protocols?						
2	Women undergoing controlled ovarian stimulation for assisted conception (IVF and/or ICSI)	Controlled ovarian stimulation protocols	Any other controlled ovarian stimulation protocol	**Primary:** - Live birth - OHSS **Secondary:** - Clinical pregnancy - Ongoing pregnancy - Multiple pregnancy - Miscarriage - Ectopic pregnancy - Cycle cancellation - Oocyte number - Cleavage-stage embryo number - Blastocyst number - Number of cryopreserved embryos	Systematic review and network meta-analysis of randomised controlled trials	Accepted
B. What is the existing evidence on the association between serum progesterone levels and FET outcomes?						
3	Women undergoing FET treatment	Optimum serum progesterone, as identified by the investigators	Serum progesterone outside the optimum range	**Primary:** - Live birth or ongoing pregnancy (composite) **Secondary:** - Clinical pregnancy - Miscarriage	Systematic review and meta-analysis of observational studies	Published

Chapter number	Population	Intervention	Comparison	Outcome(s)	Research design	Manuscript status
				- Adverse events attributable to exogenous progesterone		
C. What is the effect of the route of progesterone administration on the association between serum progesterone levels and FET outcomes?						
4	Women undergoing FET treatment	NA		**Primary:** - Live birth **Secondary:** - Implantation - Biochemical pregnancy - Clinical pregnancy - Miscarriage - Ectopic pregnancy	Multicentre observational prospective cohort study	Published
D. What is the current evidence on the effectiveness of immune therapies administered to women with subfertility and/or undergoing assisted conception?						
5	Women with subfertility and/or undergoing assisted conception	Immune therapies	Any other immune therapies, placebo, sham procedure or no intervention	**Primary:** - Live birth	Systematic review and meta-analysis of randomised controlled trials and interventional cohort studies	Published

Abbreviations: COS, controlled ovarian stimulation; FET, frozen embryo transfer; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation; NA, not applicable; OHSS, ovarian hyperstimulation syndrome.

CHAPTER 2: CONTROLLED OVARIAN STIMULATION PROTOCOLS FOR ASSISTED REPRODUCTION: A NETWORK META-ANALYSIS

Preamble

Chapter 1 outlined the principles of COS, discussed various COS protocols, and introduced network meta-analysis (NMA) for obtaining estimates from direct and indirect comparisons between multiple interventions. Chapter 2 details a Cochrane systematic review and NMA evaluating the relative effectiveness and safety of COS protocols for assisted conception. The protocol was originally published in 2017 (8). The final review manuscript has been accepted by the Cochrane Collaboration and is under editorial review.

Here I present an abridged version of the main manuscript, to abide by the University of Birmingham Regulations for word count limits in PhD theses. The format of the appended PDF follows the Cochrane Library structure and contains references separate from the main thesis. An extended version has been submitted to Cochrane, following the Collaboration's own editorial guidance. The longer version includes an extensive background section; a full description of estimated absolute risks (in percentages); and all sensitivity analyses for the primary outcomes (live birth and OHSS).

Authors' contributions

Dr Pedro Melo led all stages of the review process, including protocol revisions and approval; title and abstract screening, study selection and data extraction; quality assessment of included studies; data analysis (for pairwise comparisons and NMA); and manuscript drafting. All other contributions have been acknowledged in the manuscript.

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Cochrane Database of Systematic Reviews

Controlled ovarian stimulation protocols for assisted reproduction: a network meta-analysis (Review)

Melo P, Eapen A, Chung Y, Jeve Y, Price MJ, Sunkara SK, Mack on NS, B attacharya S, Khalaf Y, Tobias A, Broekmans FJ, Khairy M, Gallos ID, Coomarasamy A

Melo P, Eapen A, Chung Y, Jeve Y, Pri e MJ, Sunkara SK, Macklon NS, Bhattacharya S, Khalaf Y, Tobias A, Broekmans FJ, Khairy M, Gallos ID, Coomarasamy A.
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[Intervention Review]

Controlled ovarian stimulation protocols for assisted reproduction: a network meta-analysis

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ABSTRACT

Background

Controlled ovarian stimulation (COS) s an es ential step in most assisted conception cycles. It involves the administration of exogenous gonadotrophins to induce multifollicula growth, usually in addition to drugs that prevent untimely ovulation by suppressing the pituitary gland. Different treatment combinations (rmed protocols) exist in COS. These vary according to the type of drugs administered for pituitary suppression (e.g., gonadotrophin-releasing hormone [GnRH] agonists, antagonists or progestogens) and ovarian stimulation (e.g., urinary or recombinant gonadotrophins, and/or oral medications). Drug dosages, timing and routes of administration also vary between different regimens. Various randomised controlled trials (RCTs) have compared existing protocols to one another. However, there is no consensus on the relative effe t ness nd safety of COS protocols.

Objectives

We aimed to asses the re ative effectiveness and safety of COS protocols in clinical practice.

Search methods

We followed standard Cochrane methodology to conduct extensive electronic searches to July 2022.

Selection criteria

We included RCTs comparing at least two COS protocols using any form of pituitary suppression (GnRH agonists, antagonists, or progestogens); and human menopausal gonadotrophin (hMG), urinary or recombinant follicle-stimulating hormone (u/rFSH), with or without luteinising hormone (LH) and/or oral medications (e.g., clomifene or letrozole), for ovarian stimulation. The primary outcomes were the rates of live birth (LBR) and ovarian hyperstimulation syndrome (OHSS) per participant after one stimulation cycle. The secondary outcomes were the rates of ongoing pregnancy, clinical pregnancy, miscarriage, multiple pregnancy, ectopic pregnancy, and cycle

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cancellation per participant; and the number of oocytes, cleavage-stage embryos, blastocyst-stage embryos, and cryopreserved embryos per participant.

Data collection and analysis

Two reviewers independently selected studies and extracted data. We conducted pairwise and network meta-analyses (NMA) according to participants' predicted response to COS (normal, high or low). For each outcome and subgroup of women, we grouped treatment protocols into the following different networks: all pituitary suppression methods; all long GnRH agonist protocols; all short GnRH antagonist protocols; all GnRH agonist flare protocols; all protocols using progestogens for pituitary suppression; and all protocols using ovarian stimulation in the absence of pituitary suppression. Using the Cochrane Risk of Bias 1 tool, we restricted our primary analyses to RCTs at low risk of selection and other biases. We also conducted sensitivity analyses for the primary outcomes including all studies, irrespective of their risk of bias. We presented effect estimates as risk ratios (RR) for dichotomous outcomes, or mean difference (MD) for continuous outcomes, with 95% confidence intervals (CI). We considered I^2>50% as representing substantial heterogeneity. For each outcome, we generated network plots depicting all interventions in each network, and forest plots investigating direc and indirect comparisons in women with predicted normal, high and low response. We used Review Manager 5.4.1 and Stata 17 for the m ta-analyses.

Main results

We included 326 studies investigating a total of 56 different COS protocols in 57,541 women f these, 221 trials included only women with predicted normal response or whose predicted response was unstated; 28 trials includ d only women with predicted high response; and 77 trials included only women with predicted low response.

Primary outcome (effectiveness) - live birth per woman randomised

Pituitary suppression methods

In women with predicted normal response, the use of short GnRH antagonist protocols probably results in little to no difference in live birth versus long GnRH agonist protocols (RR 0.98, 95% CI 0.85 to 1.12, 6 st dies 2043 women, I^2 = 0%; moderate-certainty evidence). This suggests that if the chance of live birth following treatment with long agonis protocols is assumed to be 27%, the live birth rate with short antagonist protocols would be between 23% and 30%. For the remaining part cipant subgroups (low- and high-responding women), the evidence was of low or very low certainty.

Remaining network evidence

For the remaining networks (short GnRH antagonist protoco s, long GnRH agonist protocols, GnRH agonist flare protocols, progestogens or ovarian stimulation without pituitary suppression), the evid nce was either of low or very low certainty.

Primary outcome (safety) - OHSS per woman randomised

Pituitary suppression methods

In women with predicted normal response, the use of short GnRH antagonist protocols probably reduces OHSS versus long GnRH agonist protocols (RR 0.88, 95% CI 0.78 to 0.99, 5 s dies, 890, I^2 = 0%; moderate-certainty evidence). This suggests that if the chance of OHSS following treatment with long agonist protoc s is assumed to be 32%, the OHSS rate with short antagonist protocols would be between 25% and 32%. For the remaining par icipan subgroups (low- and high-responding women), the evidence was either of low or very low certainty.

Short GnRH antagonist protocols

In women with predicted high response undergoing short GnRH antagonist protocols, hMG probably reduces the risk of OHSS versus rFSH (RR 0.45, 95% CI 0.30 to 0 8 1 st dy, 619 women; moderate-certainty evidence). This suggests that if the chance of OHSS following treatment with rFSH is ass med to be 21%, the OHSS rate with hMG would be between 6% and 15%. For the remaining participant subgroups (normal- and low respon ing women), the evidence was of low or very low certainty.

Remaining netwo k evid nce

For the remaining netw rks (long GnRH agonist protocols, agonist flare protocols, progestogens or ovarian stimulation without pituitary suppression), the evidence was either of low or very low certainty.

Authors' conclusions

Our findings suggest that the use of short GnRH antagonist protocols probably reduces OHSS rates in women with predicted normal or high response to COS without compromising live birth rates. We were unable to meta-analyse results from 158 trials due to serious risk of selection or other biases, a lack of outcome data, or because of reporting of data in an unsuitable format for meta-analysis (e.g., per cycle); this led to underpowered analyses for several outcomes and pairwise comparisons. It also resulted in disconnected networks, limiting our

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ability to perform NMA for some outcomes. Future trials should focus on evaluating the effect of different COS protocols upon cumulative live birth rates accounting for all embryo transfers (fresh and/or frozen) after a single stimulation cycle per participant.

PLAIN LANGUAGE SUMMARY

Controlled ovarian stimulation protocols for assisted reproduction: a network meta-analysis

Review question

How effective and safe are different treatments used to stimulate the ovaries of women having in vitro fertilisation (IVF)?

Background

Infertility is common, affecting an estimated 48.5 million couples worldwide. Some people with infer ility require IVF to conceive a pregnancy. There are different steps in IVF, including: a. controlled ovarian stimulation (COS); b an egg llection procedure; c. the mixing of eggs with sperm outside the body to create embryos; and d. transferring an embryo into the woman's womb.

Controlled ovarian stimulation involves taking drugs, usually in the form of injections (called g nad trophins, including follicle-stimulating hormone [FSH] and human menopausal gonadotrophin [hMG]), to promote the growth of several ovarian follicles (fluid-filled millimetric structures which contain eggs). Ovarian stimulation aims to obtain as many eggs as p ssible i one IVF round, instead of relying on the release of one egg (ovulation) that usually occurs in a natural menstrual cycle.

In addition to stimulating the ovaries, it is often necessary to prevent the natu al release f female hormones that induce ovulation. Ovulation suppression involves giving women drugs (usually gonadotrophin-releasing hormone [GnRH] agonists, antagonists or progesterone) that suppress the pituitary gland in the brain. This is done so that clinicians can artificially trigger the maturation and release of the eggs after COS and plan the egg collection procedure. There are many treatment combinations of gonadotrophin and pituitary suppression methods; these combinations are called protocols.

Research suggests that women's predicted response to COS protocols (norm l, high or low response, usually measured by the number of eggs collected) varies according to individual characteristics, including age, bo y weight and the store of eggs in the ovaries. In addition, it is thought that COS protocols can influence the chance of achieving a pregnancy and carrying it to the birth of a live baby, but also affect the risk of developing ovarian hyperstimulation syndrome (OHSS, a po ent ally ife-threatening condition marked by excessive ovarian activity following ovarian stimulation). However, there is no consensus on h w effective and safe these protocols are in relation to each other.

Study characteristics

We included 326 studies comparing a total of 56 different COS pro ocols in 57,541 women. Of these, 221 studies included only women with predicted normal response or whose predicted respon was unstated; 28 studies included only women with predicted high response; and 77 studies included only women with predicted low respons .

Key results

Live birth

Pituitary suppression methods

Short GnRH antagonist protocols probably r sult in little to no difference in live birth when compared to long GnRH agonist protocols in women with predicted normal response. The evidence suggests that if the chance of live birth following treatment with long GnRH agonist protocols is assumed to be 27%, the live birth rate with short GnRH antagonist protocols would be between 23% and 30%. For the remaining participants (low- and high-respond ng women), the data were uncertain.

Remaining evidence

The remaining anal ses did no nfidently identify a difference in live birth between all included interventions.

OHSS

Pituitary suppression methods

In women with predicted normal response, the use of short GnRH antagonist protocols probably results in a reduction in OHSS compared with long GnRH agonist protocols. The evidence suggests that if the chance of OHSS following treatment with long GnRH agonist is assumed to be 32%, the OHSS rate with short GnRH antagonist protocols would be between 25% and 32%. For the remaining participants (low- and high-responding women), the data were uncertain.

Short GnRH antagonist protocols

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In women with predicted high response having treatment with short GnRH antagonist protocols, hMG probably reduces the risk of OHSS versus rFSH. The evidence suggests that if the chance of OHSS following treatment with rFSH is assumed to be 21%, the OHSS rate with hMG would be between 6% and 15%. For the remaining participants (normal- and low-responding women), the data were uncertain.

Remaining evidence

The remaining analyses did not confidently identify a difference in OHSS between all included interventions.

Quality of the evidence

We assessed the certainty of the evidence as ranging from very uncertain to moderately certain. Reasons for low evidence certainty were the low number of studies and patients receiving each of the 56 included treatment protocols; issues with the design of included studies (bias); variation in the results of studies assessing the same treatment comparisons (heterogeneity), an a wide range of possible effects associated with the included interventions (wide confidence intervals).

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SUMMARY OF FINDINGS

Summary of findings 1. Live birth (pituitary suppression methods - primary analysis)

Patient or population: women undergoing controlled ovarian stimulation for in vitro fertilisation

Interventions: multiple pituitary suppression methods

Comparison: any other pituitary suppression method

Outcome: live birth rate per woman randomised

Settings: assisted conception clinic or hosp al

Treatment	Di ct e idence		Indirect evidence		Anticipated absolute effects for direct estimate		
	RR 95% CI)	Certainty	RR (95% CI)	Certainty	Risk with intervention	Risk with comparator	Risk difference with intervention
Short GnRH antagonist sus lo g GnRH agonist							
Women with predicted normal response	0.98 [0.85, 1.12]	⊕⊕⊕⊖ MODERATE[a]	Unavailable	-	264 per 1000 (short GnRH antagonist)	269 per 1000 (long GnRH agonist)	**5 fewer per 1000** (from 40 fewer to 32 more)
Women with predic d high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Gn H gonist flare versus long GnRH agonist							
Women with predicted normal response	1.30 [0.96, 1.75]	⊕⊕⊖⊖ LOW[b]	Unavailable	-	477 per 1000 (GnRH agonist flare)	367 per 1000 (long GnRH agonist)	**110 more per 1000** (from 15 fewer to 275 more)
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
No pituitary suppression versus long GnRHagonist							

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Women with predicted normal response	0.94 [0.38, 2.36]	⊕⊖⊖⊖ VERY LOW [d]	U available	-	366 per 1000 (no pituitary suppression)	412 per 1000 (long GnRH agonist)	**46 fewer per 1000** (from 251 fewer to 432 more)
Women with predicted high response	Unavailable		Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
GnRH agonist flare versus short GnRH antagonis							
Women with predicted normal response	Unav ilable	-	1.33 [0.95, 1.85]	⊕⊕⊖⊖ LOW[e]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted l w r spons	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
No pituitary suppres on versus short GnRHantagonist							
Women with predicted normal response	Unavailable	-	0.69 [0.54, 0.89]	⊕⊖⊖⊖ VERY LOW[e]	See comment*	See comment**	See comment***
Women with predic ed high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
No pituit y suppression versus GnRH agonist flare							
Women with predicted normal response	Unavailable	-	0.52 [0.36, 0.75]	⊕⊖⊖⊖ VERY LOW[e]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***

*No included studies or there are no events in included studies to estimate the baseline risk.

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**Absolute risk with intervention cannot be estimated in the abs nce of abso ute risk with the comparator.

***Risk difference cannot be estimated in the absence of absolute isks with ntervention and the comparator.

CI: confidence interval; **GnRH**: gonadotrophin-releasing hormone **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the ffec estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estim te i lim ted; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little conf dence the e fect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded once because of s rious limitations in study design.
[b] Direct evidence downgraded twice because of e y serious imprecision owing to small sample size and wide confidence intervals.
[c] Direct evidence downgraded once becaus of serious inconsistency owing to high heterogeneity.
[d] Direct evidence downgraded once because of serious imprecision owing to wide confidence intervals.
[e] Indirect evidence downgraded a cord ng to the lowest of the ratings of the two direct comparisons contributing to the indirect estimate.

Summary of findings 2. L e birth (long GnRH agonist protocols - primary analysis)

Patient or population: wo en undergoing controlled ovarian stimulation for in vitro fertilisation

Interventions: m ltiple long GnRH agonist protocols

Comparison: any oth r long GnRH agonist protocol using a different gonadotrophin type than the comparator

Outcome: ve birth ate per woman randomised

Se tings: assisted conception clinic or hospital

Treat ent	Direct evidence		Indirect evidence		Anticipated absolute effects for direct estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with inter-vention	Risk with com-parator	Risk difference with intervention
Long GnRH agonist plus uFSH versus rFSH							
Women with predicted normal response	0.95 [0.76, 1.19]	⊕⊕⊕⊖ MODERATE[a]	1.21 [0.51, 2.89]	⊕⊖⊖⊖ VERY LOW[b]	258 per 1000 (long GnRH agonist plus uFSH)	271 per 1000 (long GnRH agonist plus rFSH)	**13 fewer per 1000** (from 65 fewer to 52 more)

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Women with predicted high response	1.12 [0.63, 1.99]	⊕⊕⊖⊖ LOW[c]	Unav ilable	-	238 per 1000 (long GnRH agonist plus uFSH)	213 per 1000 (long GnRH agonist plus rFSH)	**25 more per 1000** (from 79 fewer to 210 more)
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & rLH versus rFSH							
Women with predicted normal response	1.05 [0.48, 2.30]	⊕⊖⊖⊖ VERY LOW[a,d,e]	Unavailable	-	183 per 1000 (long GnRH agonist plus rFSH & rLH)	174 per 1000 (long GnRH agonist plus rFSH)	**9 more per 1000** (from 91 fewer to 226 more)
Women with predicted high response	Un vailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	0.90 [.63, 1.30]	⊕⊕⊖⊖ LOW[a,e]	Unavailable	-	106 per 1000 (long GnRH agonist plus rFSH & rLH)	117 per 1000 (long GnRH agonist plus rFSH)	**11 fewer per 1000** (from 43 fewer to 36 more)
Long GnRH agonist plus hMG versus rFSH							
Women with pred cted normal response	1.19 [0.92, 1.53]	⊕⊕⊖⊖ LOW[a,e]	0.93 [0.42, 2.05]	⊕⊖⊖⊖ VERY LOW[b]	265 per 1000 (long GnRH agonist plus hMG)	223 per 1000 (long GnRH agonist plus rFSH)	**42 more per 1000** (from 18 fewer to 118 more)
W men w th predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus letrozole & rFSH versus rFSH							
Women with predicted normal response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted high response	0.70 [0.45, 1.09]	⊕⊕⊖⊖ LOW[c]	Unavailable	-	323 per 1000 (long GnRH agonist plus letrozole & rFSH)	462 per 1000 (long GnRH agonist plus rFSH)	**139 fewer per 1000**

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							(from 254 fewer to 41 more)
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & uhCG versus rFSH							
Women with predicted normal response	1.74 [0.22, 13.79]	⊕⊖⊖⊖ VER LOW[a,c]	Unavailable	-	109 per 1000 (long GnRH agonist plus rFSH & uhCG)	63 per 1000 (long GnRH agonist plus rFSH)	**46 more per 1000** (from 49 fewer to 799 more)
Women with predicted high response	Unavaila le	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavai able	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus FSH & rhCG versus rFSH							
Women with predict d normal response	Unavailable	-	1.37 [0.50, 3.79]	⊕⊖⊖⊖ VERY LOW[b]	See comment*	See comment**	See comment***
Women with pred cted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women wit predict d low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & rLH versus uFSH							
Women with predicted normal response	Unavailable	-	1.03 [0.59, 1.82]	⊕⊖⊖⊖ VERY LOW[b]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus hMG versus uFSH							

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Women with predicted normal response	0.98 [0.51, 1.89]	⊕⊖⊖⊖ VERY LOW[a,c]	1.26 [0 5, 2.10]	⊕⊖⊖⊖ VERY LOW[b]	241 per 1000 (long GnRH agonist plus hMG)	246 (long GnRH agonist plus uFSH)	**5 fewer per 1000** (from 121 fewer to 218 more)
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable		Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & uhCG versus u SH							
Women with predicted normal response	Unavailab e	-	1.80 [0.22, 14.77]	⊕⊖⊖⊖ VERY LOW[b]	See comment*	See comment**	See comment***
Women with predicted high response	nava able	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low re sponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & rhCG versus uFSH							
Women with pred ted normal response	Unavailable	-	1.42 [0.50. 4.03]	⊕⊖⊖⊖ VERY LOW[b]	See comment*	See comment**	See comment***
Women with predicted high re- s onse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women w th predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus letrozole & rFSH versus uFSH							
Women with predicted normal response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	0.63 [0.30, 1.29]	⊕⊕⊖⊖ LOW[b]	See comment*	See comment**	See comment***

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Women with predicted low response	Unavailable	-	Unav ilable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus hMG versus rFSH & rLH							
Women with predicted normal response	Unavailable	-	1.13 [0.60, 2.12]	⊕⊖⊖⊖ VERY LOW[b]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable		Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & uhCG ve sus rFSH & rLH							
Women with predicted normal response	U available	-	1.74 [0.20, 15.04]	⊕⊖⊖⊖ VERY LOW[b]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with pred cted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & rhCG versus rFSH & rLH							
Women with predicted normal re ponse	1.38 [0.60, 3.13]	⊕⊖⊖⊖ VERY LOW[a,c]	Unavailable	-	216 per 1000 (long GnRH agonist plus rFSH & rhCG)	157 per 1000 (long GnRh agonist plus rFSH & rLH)	**59 more per 1000** (from 63 fewer to 334 more)
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & uhCG versus hMG							
Women with predicted normal response	Unavailable	-	1.54 [0.18, 12.90]	⊕⊖⊖⊖	See comment*	See comment**	See comment***

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				VERY LOW[b]			
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & rhCG versus hMG							
Women with predicted normal response	Unava lable	-	1.22 [0.41, 3.59]	⊕⊖⊖⊖ VERY LOW[b]	See comment*	See comment**	See comment***
Women with predicted high response	Unavai ble	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	nava able	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist p us rFS & rhCG versus rFSH & uhCG							
Women with predicted no mal response	Unavailable	-	0.79 [0.08, 8.08]	⊕⊖⊖⊖ VERY LOW[b]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with pr d cted low re- s onse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***

*No included studies or there are no events in included studies to estimate the baseline risk.

**Absolute risk with intervention cannot be estimated in the absence of absolute risk with the comparator.

***Risk difference cannot be estimated in the absence of absolute risks with intervention and the comparator.

CI: confidence interval; **GnRH:** gonadotrophin-releasing hormone; **hMG:** human menopausal gonadotrophin; **rFSH:** recombinant follicle-stimulating hormone; **rhCG:** recombinant human chorionic gonadotrophin; **rLH:** recombinant luteinising hormone; **RR:** risk ratio; **uFSH:** urinary follicle-stimulating hormone; **uhCG**: urinary human chorionic gonadotrophin.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

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Moderate certainty: we are moderately confident in the effect e timate; the rue effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the rue effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded once because of serious limi tio s study design.
[b] Indirect evidence downgraded according to the lowest of the atings of the two direct comparisons contributing to the indirect estimate.
[c] Direct evidence downgraded twice because of very serious imp ecision owing to small sample size and wide confidence intervals.
[d] Direct evidence downgraded once because of serious inconsistency owing to high heterogeneity.
[e] Direct evidence downgraded once because of seri us impr cision owing to wide confidence intervals.

Summary of findings 3. Live birth (short GnRH antagonist protocols - primary analysis)

Patient or population: women unde go ng controlled ovarian stimulation for in vitro fertilisation

Interventions: multiple short GnRH antago ist protocols

Comparison: any other short Gn H antagonist protocol using a different gonadotrophin type than the comparator

Outcome: live birth ra e per woman randomised

Settings: assisted concept on clinic or hospital

Treatment	Direct evidence		Indirect evidence		Anticipated absolute effects for direct estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with inter-vention	Risk with com-parator	Risk difference with intervention
Sh rt GnRH an gonist plus hMG versus rFSH							
Wom with predicted normal response	1.08 [0.89, 1.31]	⊕⊕⊖⊖ LOW[a,b]	Unavailable	-	298 per 1000 (short GnRH antagonist plus hMG)	276 per 1000 (short GnRH antagonist plus rFSH)	**22 more per 1000** (from 31 fewer to 85 more)
Women with predicted high re-sponse	1.13 [0.89, 1.42]	⊕⊕⊖⊖ LOW[a,b]	Unavailable	-	340 per 1000 (short GnRH antagonist plus hMG)	301 per 1000 (short GnRH antagonist plus rFSH)	**39 more per 1000** (from 33 fewer to 126 more)
Women with predicted low re-sponse	Unavailable	-	1.26 [0.46, 3.43]	⊕⊖⊖⊖ VERY LOW[c]	See comment*	See comment**	See comment***

Preview

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Short GnRH antagonist plus rFSH & rLH versus rFSH							
Women with predicted normal response	1.07 [0.66, 1.75]	⊕⊖⊖⊖ VERY LOW[a,d]	Unavailable	-	237 per 1000 (short GnRH antagonist plus rFSH & rLH)	221 per 1000 (short GnRH antagonist plus rFSH)	**16 more per 1000** (from 75 fewer to 166 more)
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Short GnRH antagonist plus rFSH & hMG versus rFSH							
Women with predicted normal response	Una ailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low e-sponse	0.97 [0.43, 2.20]	⊕⊕⊖⊖ LOW[a,d]	Unavailable	-	129 per 1000 (short GnRH antagonist plus rFSH & hMG)	133 per 1000 (short GnRH antagonist plus rFSH)	**4 fewer per 1000** (from 76 fewer to 160 more)
Short GnRH antagon st plus clomifene & hMG versus rFSH							
Wom n with predicted normal res onse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Wom with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	0.76 [0.14, 4.17]	⊕⊖⊖⊖ VERY LOW[c]	See comment*	See comment**	See comment***
Short GnRH antagonist plus letrozole & hMG vs rFSH							
Women with predicted normal response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***

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Women with predicted high response	Unavailable	-	Unav ilable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	3.27 [0.52, 20.69]	⊕⊖⊖⊖ VERY LOW[c]	See comment*	See comment**	See comment***
Short GnRH antagonist plus rFSH & rLH versus hMG							
Women with predicted normal response	Unavailable		0.99 [0.59, 1.68]	⊕⊖⊖⊖ VERY LOW[c]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailab e	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavai ble	-	Unavailable	-	See comment*	See comment**	See comment***
Short GnRH antagonis plu rFSH hMG versus hMG							
Women with predicted ormal response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with pred cted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women wit predic d low respon e	0.77 [0.43, 1.38]	⊕⊖⊖⊖ VERY LOW[a,d]	Unavailable	-	145 per 1000 (short GnRH antagonist plus rFSH & hMG)	188 per 1000 (short GnRH antagonist plus hMG)	**43 fewer per 1000** (from 107 fewer to 71 more)
Short Gn H antagonist plus clomifene & hMG versus hMG							
Women with predicted normal response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	0.60 [0.15, 2.39]	⊕⊕⊖⊖ LOW[d]	Unavailable	-	53 per 1000 (short GnRH antagonist plus clomifene & hMG)	88 per 1000 (short GnRH antagonist plus hMG)	**35 fewer per 1000** (from 40 fewer to 157 more)

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Short GnRH antagonist plus letrozole & hMG versus hMG							
Women with predicted normal response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	2.60 [0.55, 12.22]	⊕⊖⊖⊖ VERY LOW[a,d]	Unavailable	-	193 per 1000 (short GnRH antagonist plus letrozole & hMG)	74 per 1000 (short GnRH antagonist plus hMG)	**119 more per 1000** (from 33 fewer to 831 more)
Short GnRH antagonist plus rFSH & uhCG versus rFSH & hMG							
Women with predicted normal response	1.22 [54 2.76]	⊕⊕⊖⊖ LOW[d]	Unavailable	-	200 per 1000 (short GnRH antagonist plus rFSH & uhCG)	164 per 1000 (short GnRH antagonist plus rFSH & hMG)	**36 more per 1000** (from 76 fewer to 288 more)
Women with predicte high r sponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Short GnRH a gonist plus clomifene & hMG versus rFSH & hMG							
Women with predicted normal response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Wome with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	0.78 [0.17, 3.48]	⊕⊖⊖⊖ VERY LOW[c]	See comment*	See comment**	See comment***
Short GnRH antagonist plus letrozole & hMG versus rFSH & hMG							
Women with predicted normal response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***

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Women with predicted high response	Unavailable	-	Unav ilable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	3.36 [0.64, 17.55]	⊕⊖⊖⊖ VERY LOW[c]	See comment*	See comment**	See comment***
Short GnRH antagonist plus rFSH & uhCG versus rFSH & rLH							
Women with predicted normal response	Unavailable		Unavailable	-	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	2.00 [19, 20.67]	⊕⊖⊖⊖ VERY LOW[a,d]	Unavailable	-	80 per 1000 (short GnRH antagonist plus rFSH & uhCG)	40 per 1000 (short GnRH antagonist plus rFSH & rLH)	**40 more per 1000** (from 32 fewer to 787 more)
Short GnRH antagon st plus etrozole & hMG versus clomifene & hMG							
Women with predicted no mal response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with pred ted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Wom n with predicted low response	Unavailable	-	4.33 [0.54, 34.52]	⊕⊖⊖⊖ VERY LOW[c]	See comment*	See comment**	See comment***

*No included studies or there are no events in included studies to estimate the baseline risk.

**Absolute risk with intervention cannot be estimated in the absence of absolute risk with the comparator.

***Risk difference cannot be estimated in the absence of absolute risks with intervention and the comparator.

CI: confidence interval; **GnRH:** gonadotrophin-releasing hormone; **hMG:** human menopausal gonadotrophin; **rFSH:** recombinant follicle-stimulating hormone; **rLH:** recombinant luteinising hormone; **RR:** risk ratio; **uhCG**: urinary human chorionic gonadotrophin.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

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Moderate certainty: we are moderately confident in the effect e timate; the rue effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the rue effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded once because of serious limi tio s study design.
[b] Direct evidence downgraded once because of serious imprec sion owing to wide confidence intervals.
[c] Indirect evidence downgraded according to the lowest of the ratings of the two direct comparisons contributing to the indirect estimate.
[d] Direct evidence downgraded twice because of very seri us imprecision owing to small sample size and wide confidence intervals.

Summary of findings 4. OHSS (pituitary suppression methods - primary analysis)

Patient or population: women undergoing ontrolled ovarian stimulation for in vitro fertilisation

Interventions: multiple pituitary suppre sion methods

Comparison: any other pituitary supp ession method

Outcome: ovarian hype stimulatio syndrome rate per woman randomised

Settings: assisted co ceptio clinic or hospital

Treatment	Dire t evidence		Indirect evidence		Anticipated absolute effects for direct estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with interven-tion	Risk with compara-tor	Risk difference with inter-vention
Short GnRH antago ist versus long GnRH agonist							
Women ith predict-ed n mal response	0.88 [0.78, 0.99]	⊕⊕⊕⊖ MODERATE[a]	Unavailable	-	286 per 1000 (short GnRH antagonist)	325 per 1000 (long GnRH agonist)	**39 fewer per 1000** (from 72 fewer to 3 fewer)
Women with predict-ed high response	0.89 [0.33, 2.41]	⊕⊕⊖⊖ LOW[a,b]	Unavailable	-	40 per 1000 (short GnRH antagonist)	45 per 1000 (long GnRH agonist)	**5 fewer per 1000** (from 30 fewer to 63 more)
Women with predict-ed low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***

*No included studies or there are no events in included studies to estimate the baseline risk.

**Absolute risk with intervention cannot be estimated in the absence of absolute risk with the comparator.

***Risk difference cannot be estimated in the absence of absolute risks with intervention and the comparator.

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CI: Confidence interval; **GnRH:** gonadotrophin-releasing hormone; **RR:** Risk r tio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effe t estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is lim ted; th true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effe t estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded once because of seri us imit tions in study design.
[b] Direct evidence downgraded once because of eriou imprecision owing to wide confidence intervals.

Summary of findings 5. OHSS (long GnRH gonist protocols - primary analysis)

Patient or population: women undergo ng controlled ovarian stimulation for in vitro fertilisation

Interventions: multiple long GnRH ag nis protocols

Comparison: any other ong GnRH agonist protocol using a different gonadotrophin type than the comparator

Outcome: ovarian hy erstimulation syndrome rate per woman randomised

Settings: assisted conceptio clinic or hospital

Treatment	Direct evidence		Indirect evidence		Anticipated absolute effects for direct estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with intervention	Risk with comparator	Risk difference with intervention
L ng Gn H agonist plus uFSH versus rFSH							
Women ith predicted normal response	0.82 [0.32, 2.12]	⊕⊕⊖⊖ LOW[a,b]	Unavailable	-	41 per 1000 (long GnRH agonist plus uFSH)	50 per 1000 (long GnRH agonist plus rFSH)	**9 fewer per 1000** (from 34 fewer to 56 more)
Women with predicted high response	1.17 [0.41, 3.32]	⊕⊕⊖⊖ LOW[c]	Unavailable	-	88 per 1000 (long GnRh agonist plus uFSH)	75 per 1000 (long GnRH agonist plus rFSH)	**13 more per 1000** (from 44 fewer to 174 more)
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & rLH versus rFSH							

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Women with predicted normal response	0.15 [0.01, 2.90]	⊕⊕⊖⊖ LOW[a,b]	U available	-	4 per 1000 (long GnRH agonist plus rFSH & rLH)	25 per 1000 (long GnRH agonist plus rFSH)	**21 fewer per 1000** (from 25 fewer to 47 more)
Women with predicted high response	Unavailable		Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus hMG versus rFSH							
Women with predicted normal response	1.07 [0.6 , 1 1]	⊕⊕⊖⊖ LOW[a,b]	1.11 [0.77, 1.60]	⊕⊕⊖⊖ LOW[d]	42 per 1000 (long GnRH agonist plus hMG)	40 per 1000 (long GnRH agonist plus rFSH)	**2 more per 1000** (from 14 fewer to 28 more)
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low re ponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus SH & hMG versus rFSH							
Women with pred cted normal response	0.79 [0.42, 1.50]	⊕⊕⊖⊖ LOW[a,b]	0.84 [0.46, 1.52]	⊕⊕⊖⊖ LOW[d]	46 per 1000 (long GnRH agonist plus rFSH & hMG)	58 per 1000 (long GnRH agonist plus rFSH)	**12 fewer per 1000** (from 34 fewer to 29 more)
Women with p dicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women ith predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus letrozole & rFSH versus rFSH							
Women with predicted normal response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted high response	0.33 [0.01, 8.03]	⊕⊕⊖⊖ LOW[c]	Unavailable	-	5 per 1000 (long GnRH agonist plus letrozole & rFSH)	15 per 1000 (long GnRH agonist plus rFSH)	**10 fewer per 1000** (from 15 fewer to 109 more)

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Women with predicted low response	Unavailable	-	U available	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & uhCG versus rFSH							
Women with predicted normal response	0.35 [0.02, 5.24]	⊕⊖⊖⊖ VERY LOW[a,c]	Unavailable	-	22 per 1000 (long GnRH agonist plus rFSH & uhCG)	63 per 1000 (long GnRH agonist plus rFSH)	**41 fewer per 1000** (from 62 fewer to 265 more)
Women with predicted high response	Unavaila le	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unav ilable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & rhCG versus rFSH							
Women with predicted normal response	Una ailable	-	0.03 [0.00, 2.06]	⊕⊖⊖⊖ VERY LOW[d]	See comment*	See comment**	See comment***
Women with predicte high r - sponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonis plus rFSH & rLH versus uFSH							
Women wit predict d normal respo se	Unavailable	-	0.19 [0.01, 4.08]	⊕⊕⊖⊖ LOW[d]	See comment*	See comment**	See comment***
Wome with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus hMG versus uFSH							
Women with predicted normal response	Unavailable	-	1.35 [0.49, 3.72]	⊕⊕⊖⊖ LOW[d]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***

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Women with predicted low response	Unavailable	-	U available	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & hMG versus uFSH							
Women with predicted normal response	Unavailable	-	1.02 [0.33, 3.12]	⊕⊕⊖⊖ LOW[d]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & uhCG versus uFSH							
Women with predicted normal response	Unavailable	-	0.42 [0.02, 7.47]	⊕⊖⊖⊖ VERY LOW[d]	See comment*	See comment**	See comment***
Women with predicted high - sponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low esponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & rhCG versus uFSH							
Women with pred cted ormal response	Unavailable	-	0.04 [0.00, 2.78]	⊕⊖⊖⊖ VERY LOW[d]	See comment*	See comment**	See comment***
W men with predicted high respons	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus letrozole & rFSH versus uFSH							
Women with predicted normal response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	0.29 [0.01, 8.14	⊕⊕⊖⊖ LOW[d]	See comment*	See comment**	See comment***

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Women with predicted low response	Unavailable	-	U available	-	See comment*	See comment**	See comment***
10Long GnRH agonist plus hMG versus rFSH & rLH							
Women with predicted normal response	Unavailable	-	7.28 [0.38, 140.91]	⊕⊕⊖⊖ LOW[d]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & uhCG versus rFSH & rLH							
Women with predicted normal response	Unavailable	-	2.27 [0.04, 124.18]	⊕⊖⊖⊖ VERY LOW[d]	See comment*	See comment**	See comment***
Women with predicted high - sponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low esponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & rhCG versus rFSH & rLH							
Women with pred cted ormal response	0.20 [0.01, 4.07]	⊕⊖⊖⊖ VERY LOW[a,c]	Unavailable	-	8 per 1000 (long GnRH agonist plus rFSH & rhCG)	39 per 1000 (long GnRH agonist plus rFSH & rLH)	**31 fewer per 1000** (from 39 fewer to 121 more)
Wome with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & hMG versus rFSH & rLH							
Women with predicted normal response	Unavailable	-	5.50 [0.27, 110.42]	⊕⊕⊖⊖ LOW[d]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***

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Women with predicted low response	Unavailable	-	U available	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & hMG versus hMG							
Women with predicted normal response	0.80 [0.42, 1.54]	⊕⊕⊖⊖ LOW[a,b]	0.76 [0.42, 1.37]	⊕⊕⊖⊖ LOW[d]	46 per 1000 (long GnRH agonist plus rFSH & hMG)	57 per 1000 (long GnRH agonist plus hMG)	**11 fewer per 1000** (from 33 fewer to 31 more)
Women with predicted high response	Unavaila le		Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unav ilable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & uhCG versus h G							
Women with predicted normal response	Una ailable	-	0.31 [0.02, 4.82]	⊕⊖⊖⊖ VERY LOW[d]	See comment*	See comment**	See comment***
Women with predicte high r sponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonis plus rFSH & rhCG versus hMG							
Women wit predic d normal response	Unavailable	-	0.03 [0.00, 1.88]	⊕⊖⊖⊖ VERY LOW[d]	See comment*	See comment**	See comment***
Wome with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & uhCG versus rFSH & hMG							
Women with predicted normal response	Unavailable	-	0.41 [0.03, 6.65]	⊕⊖⊖⊖ VERY LOW[d]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***

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Women with predicted low response	Unavailable	-	U available	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & rhCG versus rFSH & hMG							
Women with predicted normal response	Unavailable	-	0.04 [0.00, 2.55]	⊕⊖⊖⊖ VERY LOW[d]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Long GnRH agonist plus rFSH & rhCG versus r SH & uhCG							
Women with predicted normal response	Unavailable	-	0.09 [0.00, 13.17]	⊕⊖⊖⊖ VERY LOW[d]	See comment*	See comment**	See comment***
Women with predicted high - sponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low esponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***

*No included studies or there are no events in included studies to estimate the baseline risk.

**Ab olute r sk with ntervention cannot be estimated in the absence of absolute risk with the comparator.

** Risk d fference cannot be estimated in the absence of absolute risks with intervention and the comparator.

CI: conf dence interval; **GnRH:** gonadotrophin-releasing hormone; **hMG:** human menopausal gonadotrophin; **rFSH:** recombinant follicle-stimulating hormone; **rhCG:** recombinant human chorionic gonadotrophin; **rLH:** recombinant luteinising hormone; **RR:** risk ratio; **uFSH:** urinary follicle-stimulating hormone; **uhCG**: urinary human chorionic gonadotrophin.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded once because of serious limitations in study design.
[b] Direct evidence downgraded once because of serious imprecision owing to wide confidence intervals.

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[c] Direct evidence downgraded twice because of very serious impre ision owing to small sample size and wide confidence intervals.
[d] Indirect evidence downgraded according to the lowest of the ratings of the two direct comparisons contributing to the indirect estimate.

Summary of findings 6. OHSS (short GnRH antagonis protocols - primary analysis)

Patient or population: women undergoing controlled ovarian st mulation for in vitro fertilisation

Interventions: multiple short GnRH antagonist protocols

Comparison: any other short GnRH antagonist pr tocol us ng a different gonadotrophin type than the comparator

Outcome: ovarian hyperstimulation syndrome r te per woman randomised

Settings: assisted conception clinic or hospita

Treatment	Di ec evidence		Indirect evidence		Anticipated absolute effects for direct estimate		
	R (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with inter-vention	Risk with com-parator	Risk difference with intervention
Short GnRH antagon st plus hMG versus rFSH							
Women with predicted no mal response	1.26 [0.65, 2.48]	⊕⊕⊖⊖ LOW[a,b]	Unavailable	-	298 per 1000 (short GnRH antagonist plus hMG)	276 per 1000 (short GnRH antagonist plus rFSH)	**22 more per 1000** (from 31 fewer to 85 more)
Women with predic ed high re-sponse	0.45 [0.30, 0.68]	⊕⊕⊕⊖ MODERATE[a]	Unavailable	-	96 per 1000 (short GnRH antagonist plus hMG)	214 per 1000 (short GnRH antagonist plus rFSH)	**118 fewer per 1000** (from 150 fewer to 69 fewer)
Women with predicted low re-sponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Short GnRH antagonist plus rFSH & rLH versus rFSH							
Women with predicted normal response	0.80 [0.22, 2.96]	⊕⊕⊖⊖ LOW[a,b]	Unavailable	-	11 per 1000 (short GnRH antagonist plus rFSH & rLH)	14 per 1000 (short GnRH antagonist plus rFSH)	**3 fewer per 1000** (from 11 fewer to 27 more)
Women with predicted high re-sponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***

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Women with predicted low response	Unavailable	-	Unava able	-	See comment*	See comment**	See comment***
Short GnRH antagonist plus rFSH & uhCG versus rFSH							
Women with predicted normal response	0.73 [0.17, 3.18]	⊕⊖⊖⊖ VERY OW[a,c]	Unavailable	-	27 per 1000 (short GnRH antagonist plus rFSH & uhCG)	37 per 1000 (short GnRH antagonist plus rFSH)	**10 fewer per 1000** (from 31 fewer to 82 more)
Women with predicted high response	Unavailable		Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Short GnRH antagonist plus rFSH & rLH ve sus hMG							
Women with predicted normal response	Unavailable	-	0.63 [0.15, 2.75]	⊕⊕⊖⊖ LOW[d]	See comment*	See comment**	See comment***
Women with predicted hig re-sponse	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with pred ted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Shor GnRH antagonist plus rFSH & uhCG versus hMG							
W men with predicted normal respo se	Unavailable	-	0.58 [0.11, 2.91]	⊕⊖⊖⊖ VERY LOW[d]	See comment*	See comment**	See comment***
Women with predicted high response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***
Short GnRH antagonist plus rFSH & uhCG versus rFSH & rLH							
Women with predicted normal response	Unavailable	-	0.91 [0.13, 6.53]	⊕⊖⊖⊖	See comment*	See comment**	See comment***

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				VERY LOW[d]			
Women with predicted high response	Unavailable	-	Una ailable	-	See comment*	See comment**	See comment***
Women with predicted low response	Unavailable	-	Unavailable	-	See comment*	See comment**	See comment***

*No included studies or there are no events n incl ded studies to estimate the baseline risk.

**Absolute risk with intervention cannot be estima ed in the absence of absolute risk with the comparator.

***Risk difference cannot be estimated i the absence of absolute risks with intervention and the comparator.

CI: confidence interval; **GnRH:** gona otrophin-releasing hormone; **hMG:** human menopausal gonadotrophin; **rFSH:** recombinant follicle-stimulating hormone; **rLH:** recombinant luteinising hormone; **RR:** ris rat o; **u CG**: urinary human chorionic gonadotrophin.

GRADE Working Group grades f evidence
High certainty: we are ery onfide t that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differen
Low certainty: our confid nce in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have v ry little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Direct evidence downgraded once because of serious limitations in study design.
[b] Direct evidence downgraded once because of serious imprecision owing to wide confidence intervals.
[c] Direc evide ce dow graded twice because of very serious imprecision owing to small sample size and wide confidence intervals.
[d] Ind rect evidence downgraded according to the lowest of the ratings of the two direct comparisons contributing to the indirect estimate.

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BACKGROUND

Description of the condition

Controlled ovarian stimulation (COS) is an essential step in many assisted reproduction technology (ART) cycles, aiming for the development of more than one ovarian follicle within a stimulation cycle to obtain several mature oocytes at the time of retrieval. There is evidence that the number of oocytes collected depends on the COS regimen administered to women, and that different COS protocols may also influence the rates of live birth and ovarian hyperstimulation syndrome (Al-Inany 2005; Siristatidis 2015; Sunkara 2011; Van Wely 2011). In addition, women's responses to COS protocols vary according to various individual characteristics, including age, body mass index, and response to previous COS (ESHRE 2020). However, there is no consensus on how different protocols relate to each other in terms of effectiveness and safety.

Description of the intervention

Controlled ovarian stimulation relies on three principles:

1. To induce the development of multiple follicles within the ovaries by administering exogenous gonadotrophins (e.g., follicle-stimulating hormone [FSH]) and/or oral medications (e.g., clomifene or letrozole).
2. To prevent untimely spontaneous ovulation by suppressing the pituitary-led endogenous luteinising-hormone (LH) surge, usually by administering gonadotrophin-releasing hormone (GnRH) analogues (agonists or antagonists) or progestogens concomitantly with stimulation drugs.
3. To trigger final oocyte maturation, usually with exogeno s human chorionic gonadotrophin (hCG) or GnRH ag nist, approximately 36 to 40 hours before oocyte retrieval (ESHRE 2020).

There are multiple ways in which gonadotrophin and pi uitary suppression drugs can be combined in COS, including

1. Long GnRH agonist protocols: GnRH agonis s are started in the mid-luteal or early follicular ph se of he me strual cycle, for a total of 10 to 14 days. O ce pitu tary suppression is diagnosed, usually by visualising a hin endometrium (<4 mm) and quiescent ovaries on transvagin l ultrasound, ovarian stimulation with exogenous gonadotrophins commences. Agonist and gonadotrophin injections are usually continued concomitantly until the day of ovulation trigger (Siristatidis 2015).
2. Short GnRH antagonist protoco s: ovarian stimulation begins in the early folli ular p ase, f llowed by GnRH antagonist initiation either once the leading follicle measures 12-14 mm on ultrasound flexib e-start regimen) or between days 4 to 6 of stimulation irresp tive of follicle size (fixed-start regimen) (Al-Inany 2005; Al-Inany 2 16).
3. GnRH agonist flare protocols: GnRH agonists are started in the early follicular phase to induce a surge of endogenous FSH, usually concurrently with gonadotrophin injections. In standard flare protocols, the agonist drug is continued until the day of trigger injection; in ultrashort flare protocols, the agonist is administered for three days and then discontinued to avoid prolonged pituitary suppression (Siristatidis 2015).
4. Protocols using progestogens for pituitary suppression: progestogens are administered with exogenous gonadotrophins from the early follicular phase until ovulation triggering (Ata 2021).
5. Protocols using gonadotrophins or oral medications in the absence of pituitary suppression drugs: ovarian stimulation is performed in the absence of pituitary suppression. The timing of trigger administration depends on follicle size on ultrasound (Zhang 2016).
6. Natural-cyle IVF: women do not receive exogenous gonadotrophins except for ovulation trigger (modified natural-cycle IVF) before oocyte retriev l in cases where a spontaneous LHS surge is not detected (Allersma 2013).

How the intervention might work

It has been suggested that long GnRH agonist protocols, there is increased synchr icity between developing ovarian follicles because of p l nged downregulation of the pituitary gland (Huirne 200). Some uthors believe that once ovarian stimulation commenc s, there is le s discrepancy in follicle growth, resulting in a more homogenous cohort which is thought improve oocyte yield in long GnRH gon t cycles (Depalo 2012). By contrast, in short GnRH antagonist protocols, research shows that follicles grow more asynch onously because of an uneven baseline follicle size in the absence of previous pituitary downregulation (Depalo 2012; Huirne 2007

Women respond differently to COS protocols according to i dividual characteristics. In its recent COS guideline, the European Soc ty of Human Reproduction and Embryology (ESHRE) made practice recommendations for ovarian stimulation according to women's predicted response to COS (normal, high or low) (ESHRE 2020). The guideline suggests that the use of antral follicle count and anti-Müllerian hormone (AMH) values should inform clinicians' judgement about women's ovarian reserve, and thus offer insight into how patients might respond to exogenous stimulation. For example, women with polycystic ovary morphology (PCOM), or an elevated age-adjusted AMH level, have a high ovarian reserve and are therefore predicted to respond strongly to COS (Teede 2018). Conversely, a reduced oocyte yield (<4) is more likely to occur in women with low age-adjusted ovarian reserve markers, or who have experienced low response to COS in a previous cycle (ESHRE 2020).

Why it is important to do this review

In the past decade, there have been several systematic reviews synthesising evidence on COS protocols. These reviews have been mostly restricted to pairwise comparisons of interventions directly evaluated against one another in randomised controlled trials (RCTs). In addition, existing reviews have focused on comparing particular components of COS protocols; for example, comparing urinary versus recombinant gonadotrophins (Van Wely 2011), oral medications versus standard gonadotrophin-based COS protocols (Kamath 2017), various GnRH agonist (Siristatidis 2015) and antagonist (Al-Inany 2016) regimens, or the addition of LH activity to FSH versus standard FSH-only stimulation (Mochtar 2007).

The diversity of systematic reviews investigating different COS components stems partly from the existence of multiple possible combinations between pituitary suppression methods and gonadotrophin types. These various permutations constitute

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an important obstacle to obtaining high-quality evidence for many of the possible comparisons due to logistical limitations involved in conducting adequately powered RCTs (Wang 2020). In recent years, this has been tackled by the development of network meta-analysis (NMA) methodology (Ioannidis 2009). With NMA, it is possible to use existing direct evidence between two interventions and a common comparator to infer indirect effect estimates between the two treatments which RCTs have not directly compared (Wang 2020).

In addition to focusing on particular aspects of COS protocols, the existing reviews largely overlook patient characteristics and predicted response to stimulation. By amalgamating women with different predicted responses into the meta-analyses, the potential effect of some interventions in specific subgroups of women may have been diluted and thus not confidently demonstrated. This has been address by a recent systematic review evaluating pairwise comparisons according to predicted response to COS, although the authors did not report a detailed assessment of the certainty of the evidence (Lambalk 2017).

There is hence a need for a systematic review including all existing COS protocols to evaluate, where possible, how each intervention compares to all others in terms of effectiveness and safety according to predicted patient response to treatment, using direct and indirect evidence. It is also necessary to evaluate the certainty of the data using robust evidence-grading tools specifically tailored to NMA estimates, so that clinicians and their patients can make informed choices based on the best available evidence (Brignardello-Petersen 2018; Puhan 2014).

OBJECTIVES

We aimed to assess the clinical effectiveness and safety of COS protocols in clinical practice. Where possible, we also aim d to generate a clinically useful ranking of these protocols.

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs or cluster trial inves igating the relative effectiveness or adverse events of OS pr tocols. We excluded cross-over, quasi-randomised and non-ra omised trials.

Types of participants

We included RCTs investigating w men undergoing COS during IVF and intracytoplasmic sperm injection (ICSI) treatment. We included all women regardless of age or xpected response to the COS protocol. We excluded studi s in which women did not undergo IVF.

Types of interven ions

We included trials omparing at least two COS protocols using GnRH agonists, an agonists or progestogens for pituitary suppression; and gonadotrophin preparations for ovarian stimulation using hMG, urinary FSH (uFSH) or recombinant FSH (rFSH), with or without LH and/or oral medications.

We conducted analyses by grouping the interventions to investigate class effects in the following manner:

1. All long GnRH agonist protocols
2. All short GnRH antagonist protocols
3. All GnRH agonist flare protocols
4. All protocols using progestogens for pituitary suppression
5. Protocols using oral medications or gonadotrophins in the absence of pituitary suppression.

We planned to create additional nodes if during the data extraction phase there were interventions that did not fit into the above groups.

We excluded trials that compared exclusively different dosages, regimens or routes of administration of the same drug and protocol.

Types of outcome mea ures

All primary and secondary ou comes were calculated per woman randomised, after the fir t fresh cycle of IVF or after the first frozen embryo transfer only in cases where fresh transfer was not undertaken. Cumulativ outcome data (e.g., cumulative live birth rate after more tha one esh or frozen embryo transfer) were not includ d. We plan ed to list outcomes where they had been presented by the auth rs in a manner that was suitable for meta-analysis, and contacted the trial authors to obtain additional data where required.

Primary outcomes

1. Li e birth (as defined by the trialists) per woman randomised;

2. Ovari n hyperstimulation syndrome (as defined by the trialists) per woman randomised.

Secondary outcomes

3. Clinical pregnancy (as defined by the trialists) per woman randomised;

4. Ongoing pregnancy (as defined by the trialists) per woman randomised;

5. Multiple pregnancy per woman randomised, counted as one live birth event;

6. Miscarriage per woman randomised;

7. Ectopic pregnancy per woman randomised;

8. Cycle cancellation (defined as a cancelled cycle before oocyte retrieval) per woman randomised;

9. Number of oocytes retrieved per woman randomised;

10. Number of cleavage-stage embryos obtained per woman randomised;

11. Number of blastocyst-stage embryos obtained per woman randomised;

12. Number of embryos frozen (or reported as being suitable for freezing) per woman randomised.

Search methods for identification of studies

We applied no language or date restrictions to our searches.

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Electronic searches

We searched the following electronic databases, trial registers and web sites in consultation with the Cochrane Gynaecology and Fertility Group (CGF) Information Specialist:

- The CGF Specialised Register of Controlled Trials (Appendix 1);
- The Cochrane Central Register of Controlled Trials (CENTRAL, *Cochrane Library*) (Appendix 2);
- MEDLINE (Appendix 3);
- Embase (Appendix 4); and
- CINAHL (Appendix 5).

The MEDLINE search was conducted with the Cochrane highly sensitive search strategy for identifying randomised trials which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). The Embase and CINAHL searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html#random).

Other electronic sources of trials included:

- Trial registers for ongoing and registered trials:
  - www.clinicaltrials.gov (a service of the United States National Institutes of Health);
  - www.who.int/trialsearch/Default.aspx (the World Health Organisation International Trials Registry Platform search portal);
- Web of Science (another source of trials and conference abstracts);
- OpenGrey - www.opengrey.eu/ for unpublished literature fr m Europe;
- LILACS and other Spanish/Portuguese databases, fo nd in the Virtual Health Library Regional Portal (VHL) regional.bvsalud.org/php/index.php?lang=en;
- PubMed and Google Scholar (for recent trials no yet inde ed in the major databases); and
- www.epistemonikos.org for other systema reviews on the subject of COS.

Searching other resources

We searched the full texts of relevant bstracts. We sought information from primary authors to investigate whether these studies met eligibility criteria, an to obtain additional outcome and study data where needed. Tri ls that compared at least two of the proposed protocols we e ligible for inclusion. We checked the reference lists of published reviews to find additional trials not identified by the sear hes.

Data collection and analysis

Selection of studies

Two review authors (PM and AE, PM and MK, or PM and YC) independently screened the titles and abstracts identified by the search, and retrieved the full texts of all potentially eligible studies. Two independent review authors (PM and AE) then examined these full-text articles for compliance with the inclusion criteria and selected eligible studies. We corresponded with study investigators as required, to clarify study eligibility. We resolved any disagreements through discussion or, if required, in consultation with a third author (AC). For reports requiring translation, we used the assistance of volunteers within the Cochrane Collaboration (see Acknowledgements) or used Google Translate (translate.google.com). Multiple reports of the same study were collated under a single reference. We created a table of excluded studies, with reasons for exclusion. We documented the selection process with a Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow chart.

Data extraction and management

We designed an electronic form in Microsoft Access to extract data. For included studies, two review authors (PM and AE) independently extracted data using the agreed form. We resolved discrepancies through discussion an consensus. We entered data into Review Manager 5.4 software (RevMan 2020) and checked data for accuracy. When info ation r garding study data was unclear, we attempted to contact th authors of the original reports to obtain further details.

Outcome data

From each ncluded study we extracted the number of participants, the age and th mai cause of infertility, and any exclusion criteria. We also extracted the interventions being compared, and the primary and secondary outcomes. All relevant arm-level data were extracted (e.g., number of events and number of patients for binary o tcomes; and mean, standard deviation and number of participants for continuous outcomes).

D ta on potential effect modifiers

From each included study we extracted the following study, tervention and population characteristics that might have acted as effect modifiers:

- Predicted response (normal, high or low).
- Age, body mass index and ethnicity (as described in the inclusion and exclusion criteria).
- Dosage, regimen, and route of drug administration.

Other data

We extracted the following additional data from each included study: country or countries in which the study was performed; date of publication; type of publication (full-text publication, abstract publication, unpublished data); and trial registration number.

Assessment of risk of bias in included studies

Two review authors (PM and AE) independently assessed the risk of bias of each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022), as described below. We resolved any disagreement by discussion and consensus.

1. Random sequence generation (checking for possible selection bias)

For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We excluded studies with high risk of bias for sequence generation (any non-random process, e.g., odd or even date of birth; hospital or clinic record number).

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Based on the methods described for each study, we assessed its risk of bias as:

- Low (any truly random process, e.g., random number table; computer random number generator); or
- Unclear.

2. Allocation concealment (checking for possible selection bias)

For each included study, we described the method used to conceal allocation to interventions before assignment. We assessed whether intervention allocation could have been foreseen before or during assignment.

Based on the methods described for each study, we assessed its risk of bias as:

- Low (e.g., telephone or central randomisation; sealed, consecutively numbered opaque envelopes [SNOSE]);
- High (e.g., open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- Unclear.

3.1 Blinding of participants, and personnel (checking for possible performance bias)

For each included study, we described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies to be at low risk of bias if they were blinded, or if we considered that the lack of blinding would be unlikely to affect results.

Based on the methods described for each study, we assessed its risk of bias as:

- Low, high or unclear.

3.2 Blinding of outcome assessment (checking for po ible detection bias)

For each included study, we described the methods u ed if any, to blind outcome assessors from knowledge of wh ch intervention a participant received. We assessed blind ng s parately for different outcomes. We considered that stud es were at low risk of bias if they blinded the outcome assesso s or f we judged that the lack of blinding would be unlikely to affe t results. For example, lack of blinding of the outcome assessors is nlikely to introduce detection bias in this context with an objective outcome such as live birth and multiple pregnancy. However, blinding might influence outcomes for other adverse events s ch as OHSS events or cycle cancellations.

Based on the metho s describ d for each study, we assessed its risk of bias as:

- Low, high or unclea

4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For each included study, and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or was supplied by the trial authors, we re-included missing data in the analyses.

Based on the methods described for each study, we assessed its risk of bias as:

- Low (e.g., no missing outcome data; missing outcome data balanced across groups or not exceeding 10% for the primary outcomes of the review);
- High (e.g., numbers or reason for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of interven on received from that assigned at randomisation or exceeding 10% fo the primary outcomes of the review); or
- Unclear.

5. Selective reporting (checking for reporting bias)

We search d for within rial selective reporting, such as trials failing to report ob ous out omes, or reporting them in insufficient detail to allow inclusion. We sought published protocols and compared the outcomes between the protocol and the final published study. To resol e any discrepancies, we attempted to contact authors of the or gina reports for further details.

Ba d o the methods described for each study, we assessed its risk f bias as:

- Low (where it was clear that all the study's prespecified outcomes and/or most expected outcomes of interest to the review were reported);
- High (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified in the trial registration record; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported); and
- Unclear.

6. Other biases (checking for bias due to problems not covered by items 1 to 5 above)

For each included study, we described any important concerns we had about other possible sources of bias. Specifically, we contacted study authors to obtain additional data, and judged trials to be at a high risk of other biases in the following cases:

- Single-centre trials reporting an implausibly high recruitment rate;
- Trials published from 2010 onwards where details of registration were not provided, or where registration was undertaken ≥6 months after recruitment started;
- Trials reporting an effect size ≥2 times higher in one of the arms for the primary outcomes of live birth and OHSS.

We assessed whether each study was free of other problems that could put it at risk of bias, and rated each study as:

- Low risk of other bias;
- High risk of other bias; or

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- Unclear whether there was risk of other bias.

Measures of treatment effect

For dichotomous data, we presented results as a summary risk ratio (RR) with 95% confidence intervals (CIs). For continuous data, we reported effect estimates as the mean difference (MD) with 95% CIs.

Relative treatment ranking

We planned to estimate the ranking probabilities for all treatments of being at each possible rank for each intervention. We also planned to obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA). SUCRA can also be expressed as a percentage of effectiveness or side effects of a treatment that would be ranked first without uncertainty.

Unit of analysis issues

The primary analysis was per woman randomised. Multiple live births (e.g., twins or triplets) were counted as one live birth event. Where studies reported only 'per cycle' data, we contacted the authors and requested 'per woman' data.

Dealing with missing data

For included studies, we noted levels of attrition. We used sensitivity analysis to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect. For all outcomes, we performed analyses, as far as possible, on an intention-to-treat basis, i.e., we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which the were allocated, regardless of whether they received the allocated intervention. The denominator for each outcome in each trial w s the number randomised.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneit

To evaluate the presence of clinical hetero eneit , we generated descriptive statistics for trial and study population characteristics across all eligible trials h t dir ctly compared each pair of interventions. We assessed the presence of clinical heterogeneity within each pairwise c mparis n by evaluating these characteristics.

Assessment of transitivity across treatment comparisons

We assessed the transitivity sumption by comparing the distribution of potential effect modifiers across the different pairwise comparisons. In this c ntext, we expected that the transitivity assumption wou d hold, ssuming the following:

1. The common COS pro ocol used to compare different protocols indirectly was s mila when it appeared in different comparisons (e.g., *Long GnRH pr tocol plus HMG* is administered similarly in the comparison of *Long GnRH protocol plus HMG* versus *GnRH agonist flare plus hMG* and in the comparison of *Long GnRH agonist plus HMG* versus *Short GnRH antagonist plus HMG*).
2. All pairwise comparisons did not differ regarding the distribution of effect modifiers (e.g., the design and study characteristics of *Long GnRH agonist plus hMG* versus *GnRH agonist flare plus HMG* trials are similar to *Long GnRH agonist plus hMG* versus *Short GnRH antagonist plus hMG*).

We evaluated the assumption of transitivity epidemiologically by comparing the clinical and methodological characteristics of sets of studies grouped by treatment comparisons and by the predicted response to COS.

Assessment of statistical heterogeneity and inconsistency

Assumptions when estimating heterogeneity

In standard pairwise meta-analyses, we estimated different heterogeneity variances for each pairwise comparison. In network meta-analysis, we assumed a common estimate for the heterogeneity variance across th different comparisons.

Measures and tests for heterogeneity

We assessed the presence of heterogen ity statistically within each pairwise comparison using the I^2 stat stic. We judged I^2>50% as representing substant al het rogeneity.

The assessme f statis ical heterogeneity in the entire network was based on the magnitude of the heterogeneity variance paramete (τ^2) estimat d from the network meta-analysis models.

Assessment of tatisti al inconsistency

We evaluated the statistical agreement between the various sources of evidence in a network of interventions (consistency) by global and local approaches to complement the evaluation of trans tivity (Higgins 2012).

Assessment of reporting biases

Give the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert to duplication of data. In addition, we planned to use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies) if there were ten or more studies in the network meta-analysis.

Data synthesis

Methods for direct treatment comparisons

We performed standard pairwise meta-analyses using a random-effects model on Review Manager, or a fixed-effect model in Stata for networks containing such a low number of events that the software could not perform a random-effects model (Der Simonian 1986; White 2015).

Methods for indirect and mixed comparisons

We performed network meta-analysis using a random-effects model in Stata using the 'network' command for network meta-analysis (White 2015) and other Stata commands for visualising and reporting results in network meta-analysis (Chaimani 2015).

Subgroup analysis and investigation of heterogeneity

We restricted our primary analysis to studies judged to be at low risk of selection and other biases. We stratified all effects according to the predicted response (women with predicted normal/unstated, high, and low response as defined by the trialists) to explore whether comparative effectiveness and safety would vary according to the predicted response. For each subgroup of

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participants, we planned the analyses by grouping interventions in the following manner:

1. All long GnRH agonist protocols
2. All short GnRH antagonist protocols
3. All GnRH agonist flare protocols
4. All protocols using progestogens for pituitary suppression
5. Protocols using oral medications and/or gonadotrophins in the absence of pituitary suppression.

We planned to consider creating additional nodes if we identified interventions that did not fit into the above groups during the data extraction phase.

We assessed subgroup differences by interaction tests available within Stata. We reported the results of subgroup analyses quoting the Chi^2 statistic and *P* value, and the interaction test I^2 value.

We planned to assess subgroup differences by evaluating the relative effects and assessing the model fit for the primary outcomes. Multi-arm trials that compared different dosages, regimens or routes of drug administration within one protocol, but also compared those versus another protocol, were included. Intervention arms of different dosages, regimens or routes of the same drug were merged for the main analysis.

Sensitivity analysis

For the primary outcomes (live birth and OHSS), we planned to conduct sensitivity analysis for the following:

- inclusion of all studies regardless of the risk of selection bias (low and unclear) and other biases (low, high and unclear);
- randomisation unit (cluster versus individual);
- use of fixed-effect versus random-effects model; and
- different effect measures (odds versus risk ratio).

Summary of findings and assessment of the certainty of the evidence

We created 'Summary of findings' (SOF) tables using GRADEpro software (GRADEpro GDT 2022) for the primary outcomes of live birth and OHSS. Each SOF table included all interventions within a network of COS protocols, where possible (e.g., pituitary suppression methods, long GnRHa agonist protocols, or all short GnRH antagonist protocols). Where possible, we provided direct and indirect estimates for all available comparisons. We used GRADE methodology to rate the certainty of the direct evidence according to study design limitations/overall risk of bias, inconsistency, imprecision, indirectness and publication bias (Higgins 2022). Where applicable, w also graded the certainty of the indirect evidence acco ding to the ower certainty ratings of the two direct arms connecting th dominant "first-order" loop in the network diagram for a par icular outcome (Brignardello-Petersen 2018; Puhan 2014).

The certain y of th evide ce was rated as "high", "moderate", "low", or " ery low" according to GRADE methodology (GRADEpro GDT 2022) We docum nted justifications for all our judgements about evide ce certainty in the SOF tables.

RESULTS

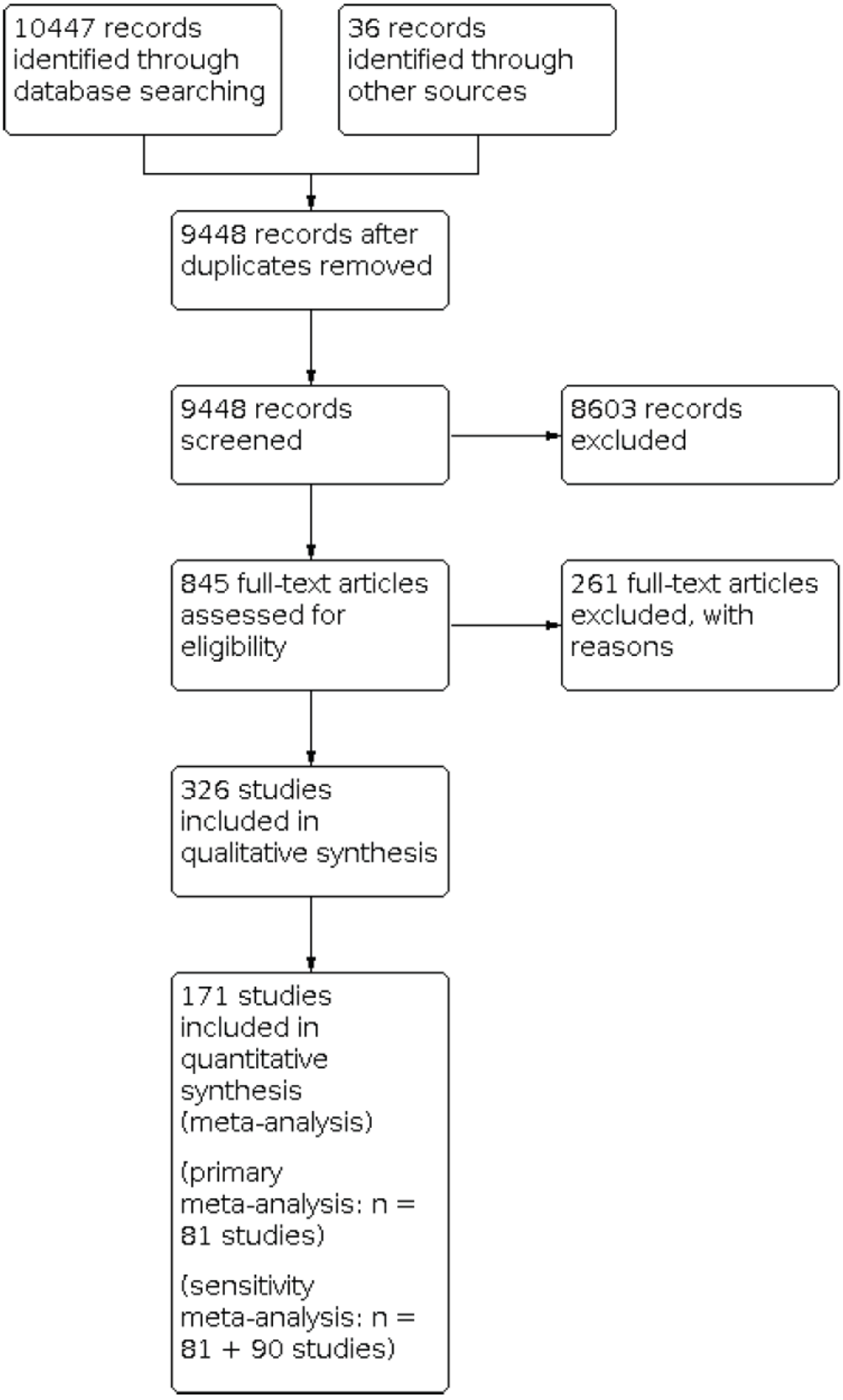
De ription of studies

Result of the search

F gure 1 shows the PRISMA flow diagram. The electronic searches con ucted on 12 July 2022 identified 10,447 studies. Following the removal of 999 duplicates, we screened the titles and abstracts of 9,448 studies, of which we excluded 8,579 because they were irrelevant. We did not find the full-text or abstract versions of 24 articles despite assistance from Cochrane in attempting to retrieve these records, and therefore we excluded these trials. We reviewed 845 full-text references, of which we excluded 261 (for reasons, see Characteristics of excluded studies). A total of 222 studies are awaiting classification (Characteristics of studies awaiting classification), and 36 studies are ongoing and have not yet reported their results (Characteristics of ongoing studies).

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Figure 1. Study selection process.



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We identified 326 studies that fulfilled this review's eligibility criteria and were included in the qualitative analysis. Of these, we included 81 studies in our primary quantitative analysis evaluating solely trials at low risk of selection and other biases, and an additional 90 trials in our sensitivity analysis including all studies independently of their risk of bias. The remaining 158 included studies were not suitable for meta-analysis because of how they presented outcome data (e.g., per cycle rather than per participant randomised) or because they did not report data on the primary outcomes of this review and were thus unsuitable for sensitivity analysis (Characteristics of included studies).

Included studies

Study design and setting

The Characteristics of included studies table contains a detailed description of included studies. We included 326 randomised controlled trials, among which there were 274 published full-text manuscripts, 48 conference abstracts, 2 trial reports, and 2 trial registration records presenting outcome data. The included studies were conducted in 39 countries. A total of 254 studies were conducted in a single centre; 63 were multicentre trials; and 9 studies did not state the number of centres involved in patient recruitment. Thirty-four trials were registered prospectively, 37 were registered retrospectively or late (>6 months of recruitment initiation), and the remaining trials were either unregistered or had an unclear registration timeline.

Participants

The included studies evaluated a total of 57,541 randomise participants, of whom we included 37,018 in the quan itative synthesis. Most studies (n = 314) evaluated COS in women havi g treatment with their own oocytes, and 12 evaluated donor o cyte cycles. A total of 221 trials included solely women with predic ed normal/unstated response; 28 trials included only participants i predicted high response; and in 77 trials the participants esponse to stimulation was predicted as low.

Interventions

The included studies evaluated 56 different COS protocols distributed across the following five categorie :

- Long GnRH agonist protocols (n = 344 ms)
- Short GnRH antagonist protocols (n = 219 a ms)
- GnRH agonist flare protocols (n = 74 arms)
- Protocols using progestogens f r pituitary suppression (n = 8 arms)
- Ovarian stimulation without pitu ary suppression (n = 39 arms).

There were 23 tria s with more than two arms where a similar (varying only in route dose or frequency of administration) protocol was used i more than one arm. For the purposes of meta-analysis, we merged arms evaluating the same intervention within each of these studies where possible, and documented this in the Characteristics of included studies table.

Among studies evaluating non-donation cycles, 84 used ICSI only; 17 used conventional IVF only; 115 used either IVF or ICSI; and in 98 trials the fertilisation method was unstated.

A total of 205 studies reported on embryo age at the time of transfer. Of these, 170 used cleavage-stage embryos; 21 studies used embryos of various ages (including cleavage-stage and blastocysts); 10 used blastocysts exclusively; and in one study only pronuclear-stage embryos were transferred. The remaining studies did not specify embryo age at the time of transfer.

Among studies reporting on the regimens administered for luteal phase support (LPS) in fresh transfer cycles, 119 used exclusively vaginal progesterone; 49 used intramuscular progesterone, vaginal progesterone or a combination of these two routes; 17 used hCG alone; 15 used hCG alone, progesterone alone or a combination of these two drugs; 2 each used a combination of oral dydrogesterone and vaginal progesterone, oral micro ized progesterone or various routes of progesterone; and 1 each used progesterone injections and rectal progesterone In six tudies, all participants underwent cryopreservation of al emb yos.

Outcomes

Primary ou comes

Eighty-two studies reported on the primary effectiveness outcome (live birth), o which 1 were included in the meta-analysis; and 94 trials reported on the primary safety outcome (OHSS), of which 83 were included in the meta-analysis.

Sec dary utcomes

total of 171 trials reported on clinical pregnancy (54 included in the meta-analysis); 92 trials reported on ongoing pregnancy (5 included in the meta-analysis); 50 trials reported on multiple pregnancy (21 included in the meta-analysis); 105 trials reported miscarriage (41 included in the meta-analysis); 24 trials reported on ectopic pregnancy (13 included in the meta-analysis); 139 trials reported on cancellation (60 included in the meta-analysis); 286 trials reported on oocyte number (69 included in the meta-analysis); 24 trials reported on cleavage-stage embryo number (5 included in the meta-analysis); 7 studies reported on blastocyst number (5 included in the meta-analysis); and 50 trials reported on the number of cryopreserved embryos (19 included in the meta-analysis).

Author correspondence

We contacted the authors of 247 studies to clarify study characteristics and determine whether they were suitable for inclusion, as well as to seek additional outcome data. To date, we have received replies from the authors of 18 studies (Ashrafi 2011; Cheung 2005; Cota 2012; Franco 2003; Fusi 2020; Giles 2021; Liu 2020; Lukaszuk 2015; Papanikolaou 2012; Ragni 2012; ACTRN12616001539426 2016; D'Amato 2004; Gomes 2007; Martinez 2003; NCT02471677 2015; NCT03423537 2019; NCT03809221 2019; Siristatidis 2017).

Excluded studies

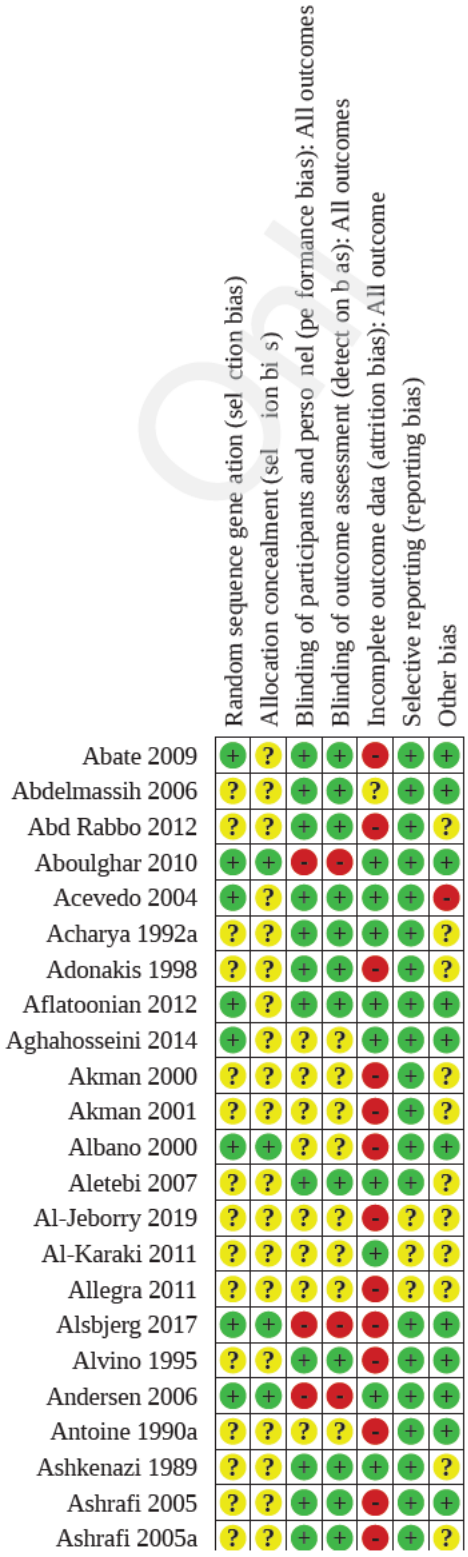
We excluded 261 studies. The Characteristics of excluded studies table provides details of reasons for exclusion.

Risk of bias in included studies

Figure 2 and Figure 3 summarise our assessment of the risk of bias in all included studies. The Characteristics of included studies table contains a detailed description of our evaluation.

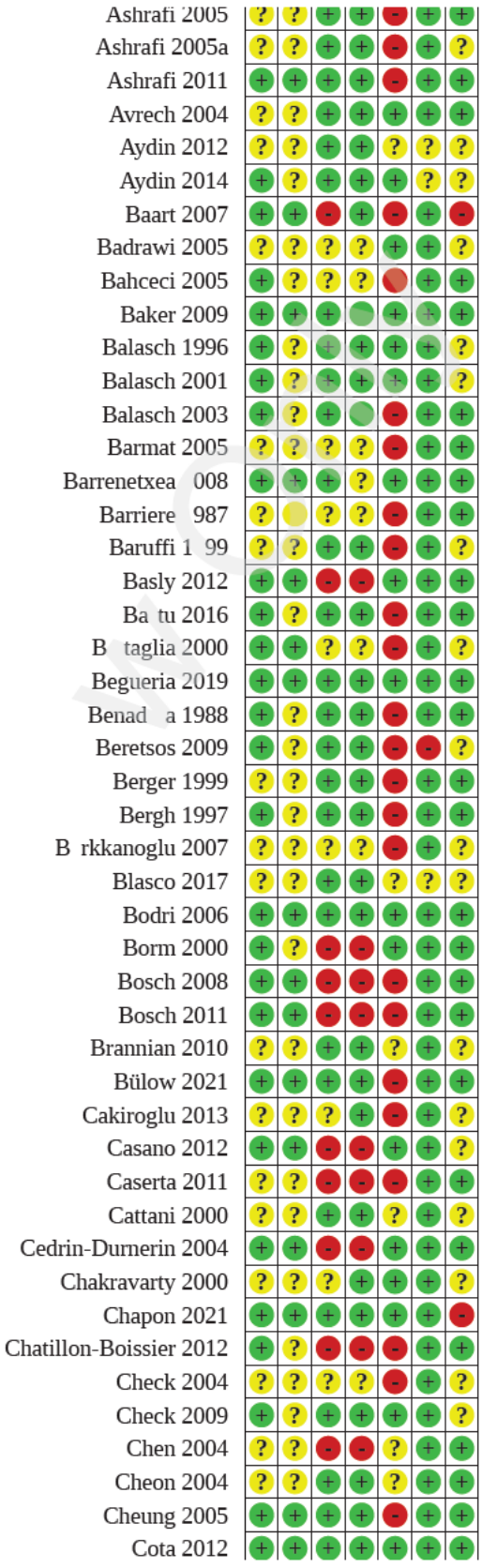
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Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



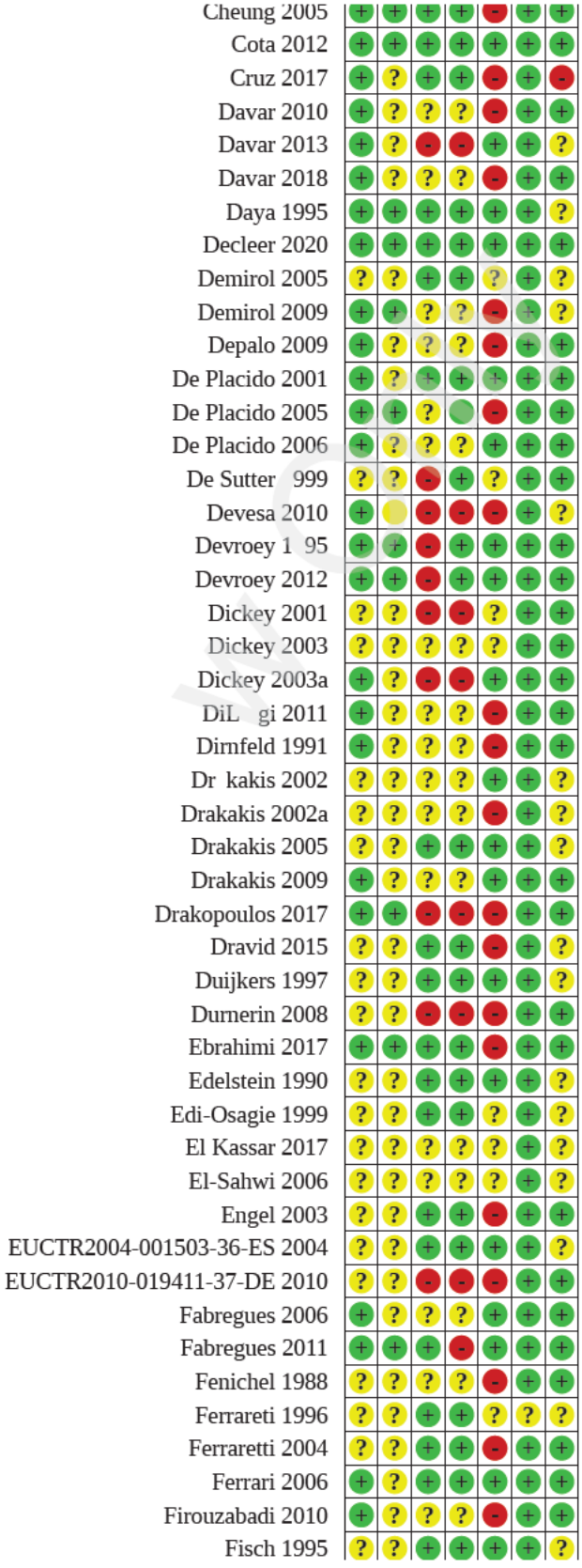
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Figure 2. (Continued)



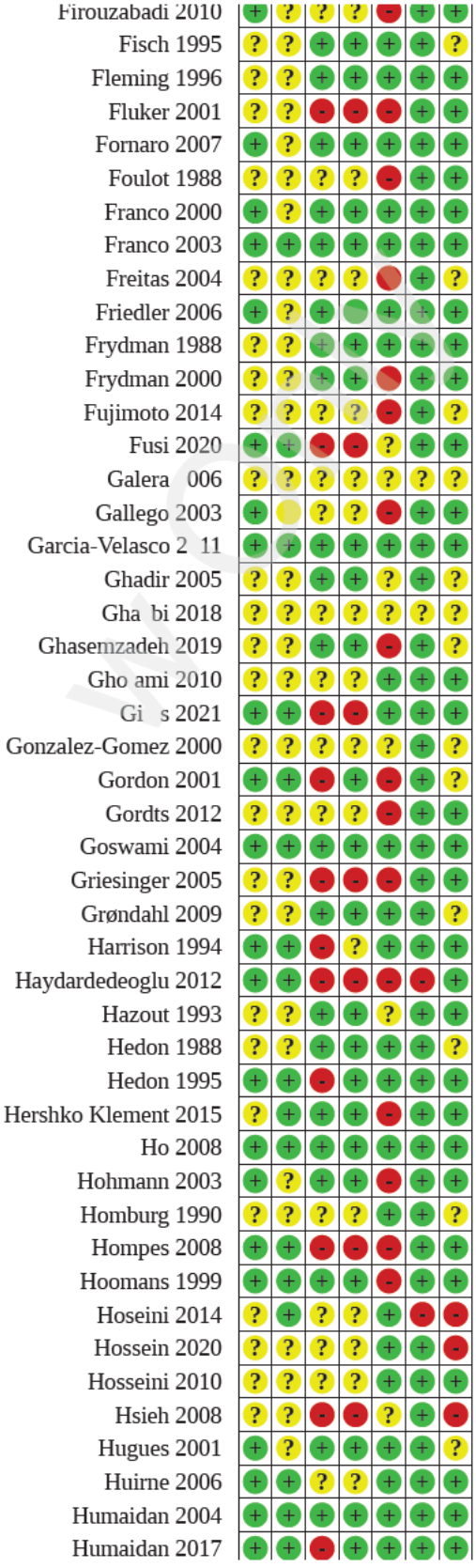
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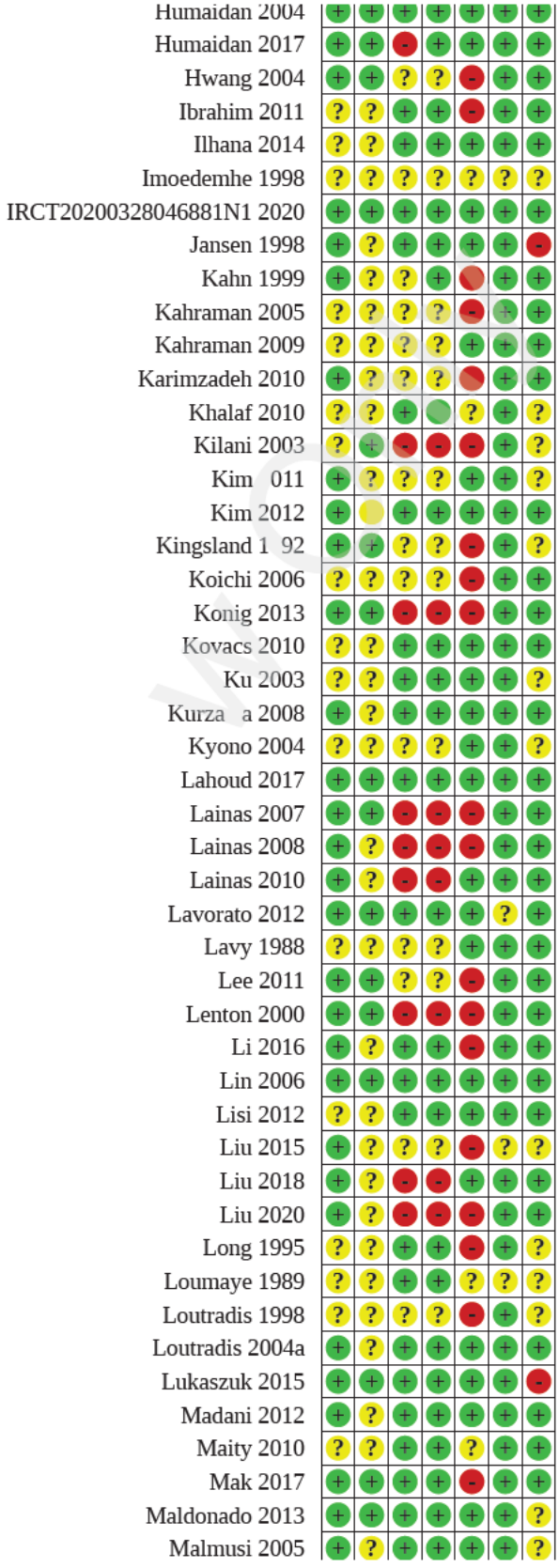
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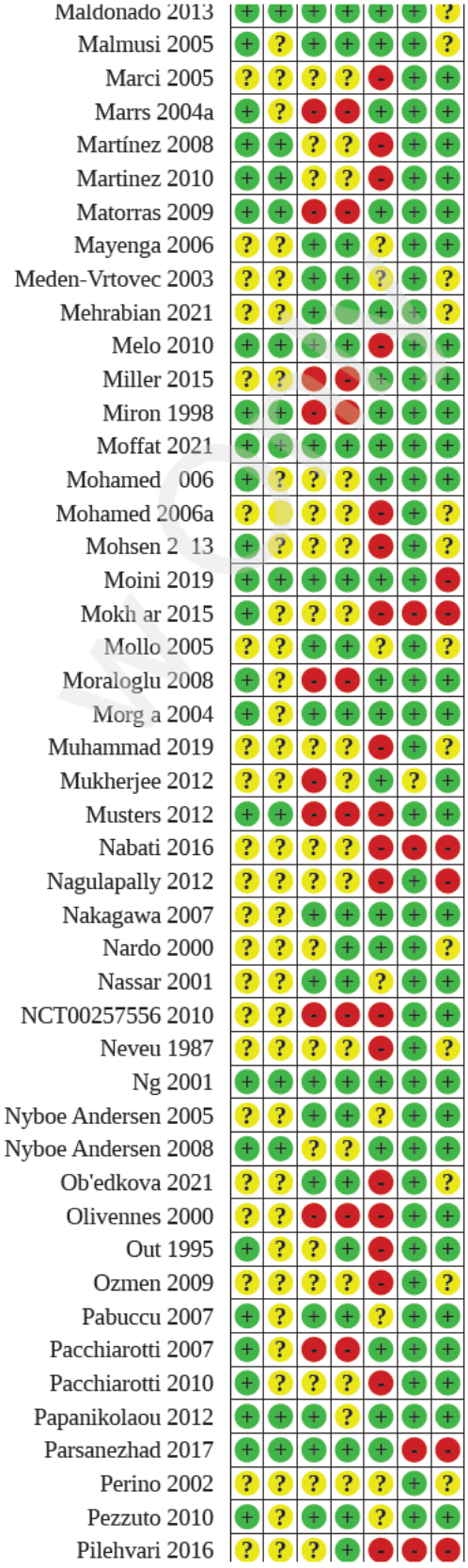
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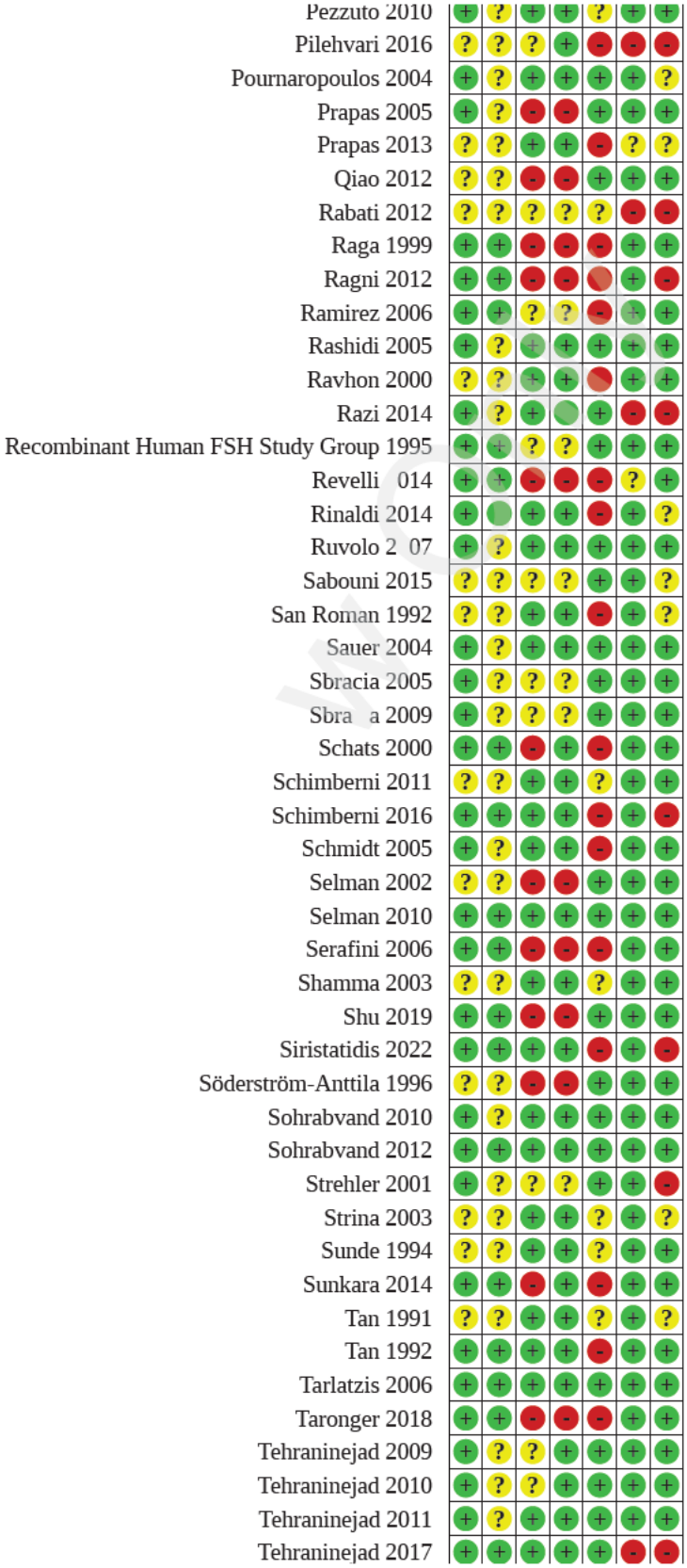
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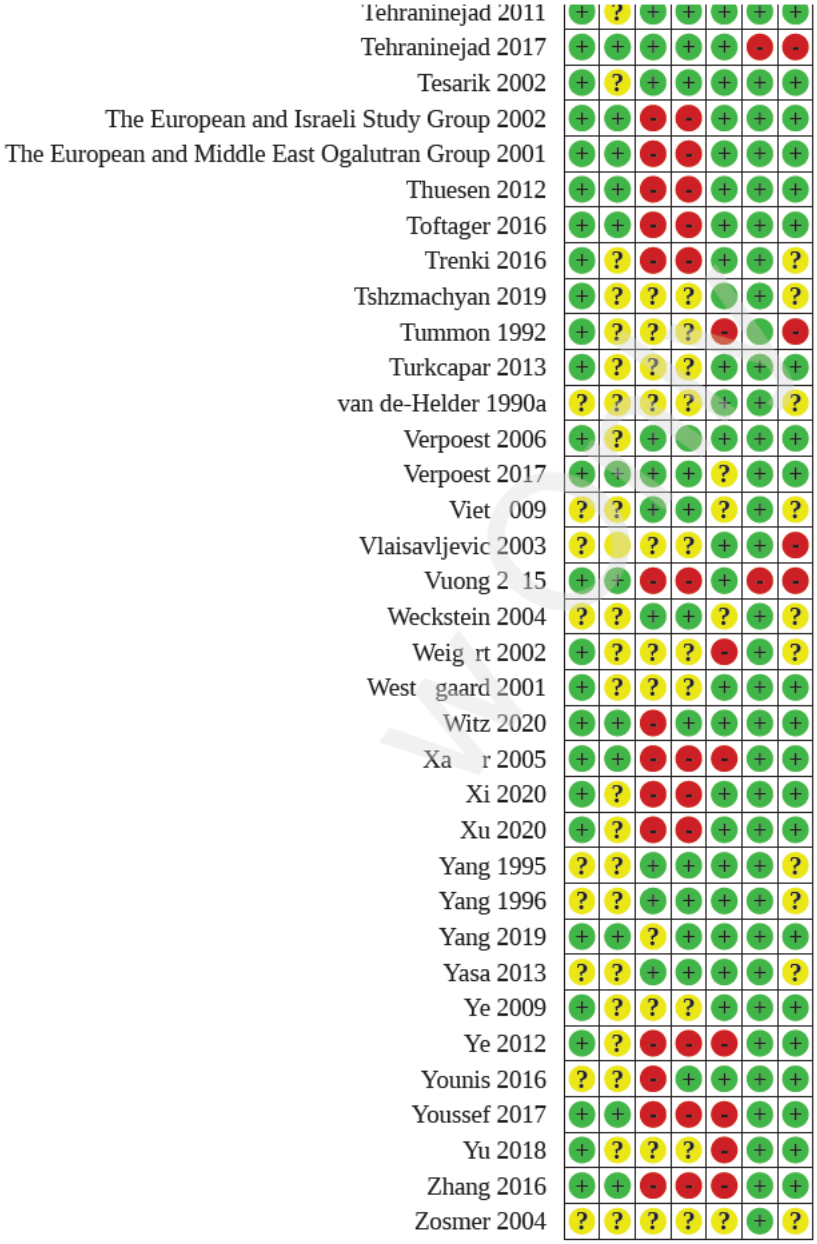
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Figure 2. (Continued)



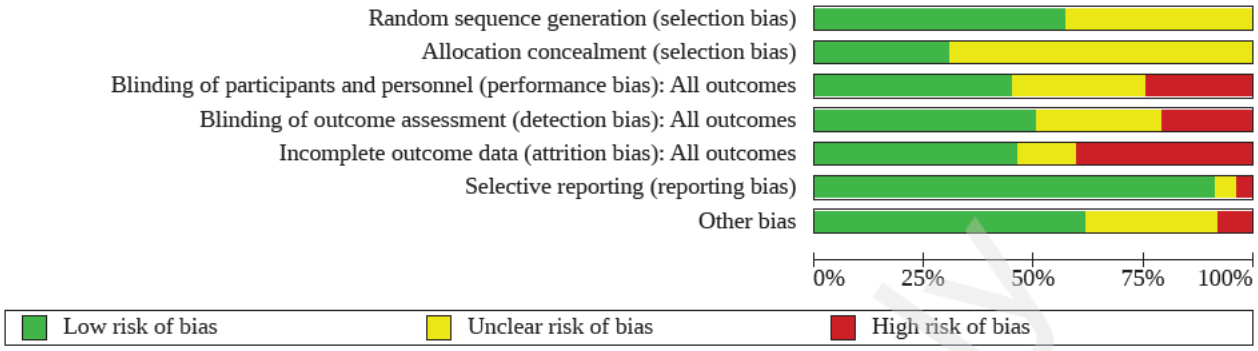
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Figure 2. (Continued)



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Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

We found that 189 of 326 trials (58%) used adequate methods for sequence generation, and were thus judged to be at low risk of bias. The risk of bias associated with sequence generation was found to be unclear in the remaining 137 trials (42%). This was usually because investigators did not state which methods had been used for sequence generation and randomisation.

A total of 102 of 326 trials (31%) used adequate methods for allocation concealment (e.g., SNOSE, central allocation management), whereas in the remaining 224 trials (69%) the methodology employed for allocation concealment was not clearly specified.

Blinding

We judged double-blind studies and trials investigating exclusively objective outcomes (e.g., live birth or oocyte number) to be at low risk of performance bias (149 of 326, 46%). In 99 of 326 trials (30%), the investigators reported subjective outcomes but blinding of participants and personnel was unstated; we judged these trials to be at unclear risk of performance bias. The remaining 78 trials (24%) had an open design, and the risk of performance bias was judged to be high because of the reporting of subjective outcomes (e.g., OHSS, cancellation).

In 167 of 326 trials (51%), the investigators confirmed blinding of outcome assessors or reported exclusively objective outcomes, and we judged the risk of detection bias to be low. The risk of detection bias was judged to be high in 64 trials (20%) due to an open design and reporting of subjective outcomes. In the remaining 95 trials (29%), the risk of detection bias was unclear due to a lack of data on blinding of outcome assessors.

Incomplete outcome data

We judged 150 of 326 trials (46%) to be at low risk of attrition bias because they reported low attrition rates (<10%) and performed an intention-to-treat (ITT) analysis. In 132 trials (40%), the risk of attrition bias was considered high due to high attrition rates and/or lack of ITT analysis. In the remaining 44 trials (14%), the authors provided insufficient data on attrition and/or unit of analysis ("per woman" or "per cycle"), and we judged these studies to be at unclear risk of attrition bias.

Selective reporting

In most of the included trials (n = 299, 92%), we did not detect evidence of selective reporting, and judged the risk of reporting bias to be low. Eleven studies (3%) were judged to be at high risk of reporting bias due to retrospective registration. The remaining 16 trials (5%) were judged to be at unclear risk of reporting bias, mostly because of insufficient details about trial registration.

Other potential sources of bias

In total, 199 of 326 trials (61%) were judged to be at low risk of other biases, owing to adequate prospective registration, plausible recruitment rates, no concerns regarding the validity of results, and plausible effect size differences between study arms. In 25 trials (8%) that clearly failed to fulfil one or more of the aforementioned criteria, the risk of other biases was judged to be high. In the remaining 102 trials (31%), there was a lack of detail on trial registration, recruitment rates and/or effect size differences between arms, and these trials were thus judged to be at unclear risk of other biases.

Effects of interventions

See: **Summary of findings 1** Live birth (pituitary suppression methods - primary analysis); **Summary of findings 2** Live birth (long GnRH agonist protocols - primary analysis); **Summary of findings 3** Live birth (short GnRH antagonist protocols - primary analysis); **Summary of findings 4** OHSS (pituitary suppression methods - primary analysis); **Summary of findings 5** OHSS (long GnRH agonist protocols - primary analysis); **Summary of findings 6** OHSS (short GnRH antagonist protocols - primary analysis)

Primary outcomes

1. Live birth

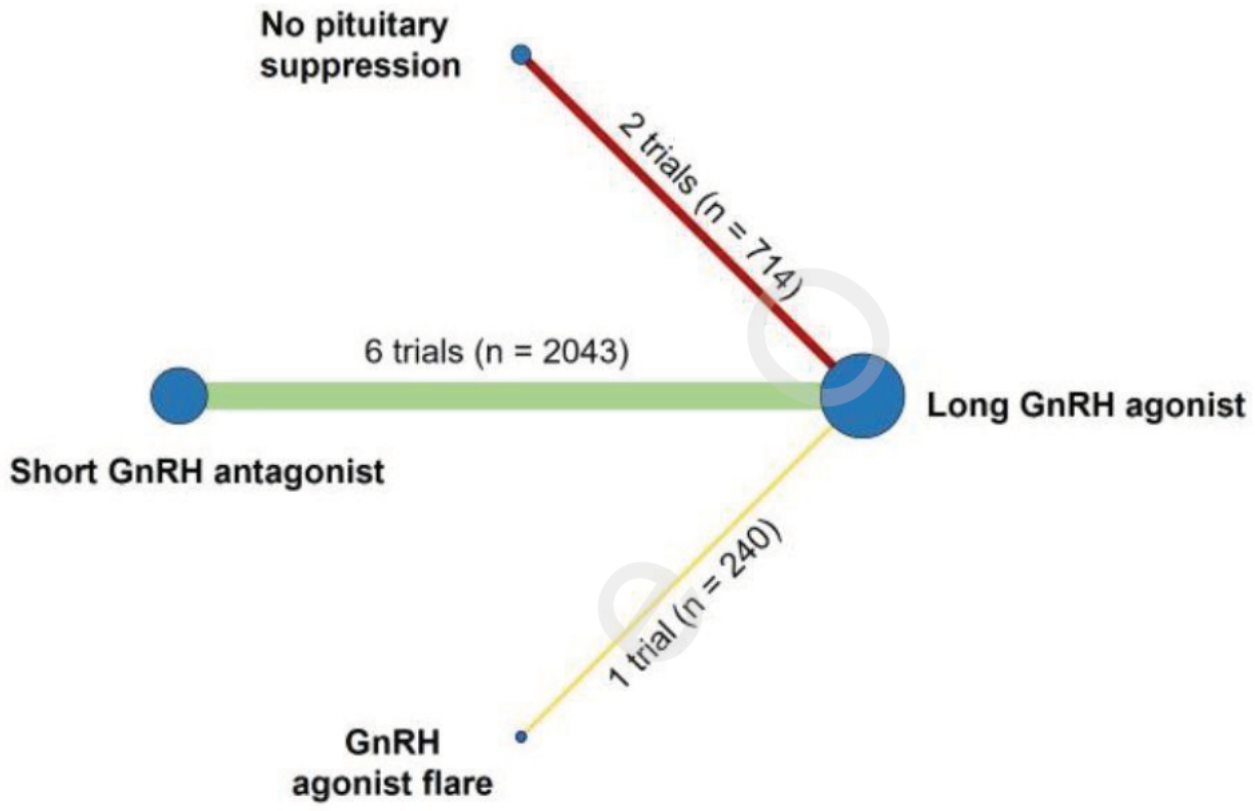
1.1. Women with predicted NORMAL response

Pituitary suppression methods – primary analysis

Figure 4 shows the primary network diagram of pituitary suppression methods for live birth in women with predicted normal response. The network was connected. There were three direct comparisons and three indirect comparisons.

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Figure 4. Primary analysis: network diagram of pituitary suppression methods for the outcome of live birth in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is light green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

Short GnRH antagonist versus long GnRH agonist

In women with predicted normal response, short antagonist protocols probably result in little to no difference in live birth versus long agonist protocols (RR 0.98, 95% CI 0.85 to 1.12, 6 studies, 2043 women, I^2 = 0%; moderate-certainty evidence; Analysis 1.1).

GnRH agonist flare versus long GnRH agonist

GnRH agonist flare protocols may result in little to no difference in live birth versus long agonist protocols (RR 1.30, 95% CI 0.96 to 1.75, 1 study, 240 women; low certainty evidence; Analysis 2.1).

No pituitary suppression versus long GnRH agonist

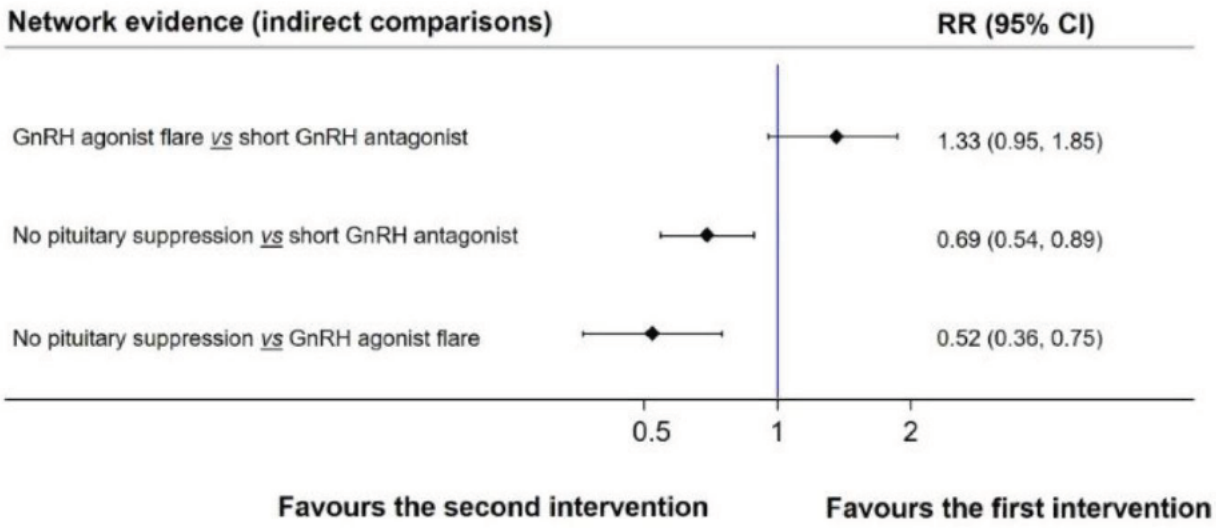
The evidence is very uncertain about this comparison (RR 0.94, 95% CI 0.38 to 2.36, 2 studies, 714 women, I^2 = 85%; very low-certainty evidence; Analysis 3.1).

Network estimates (indirect evidence only)

For the three remaining indirect comparisons, the network evidence is either uncertain or very uncertain (for effect estimates, see Figure 5).

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Figure 5. Primary analysis: forest plot comparing pituitary suppression methods with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of live birth in women with predicted normal response.

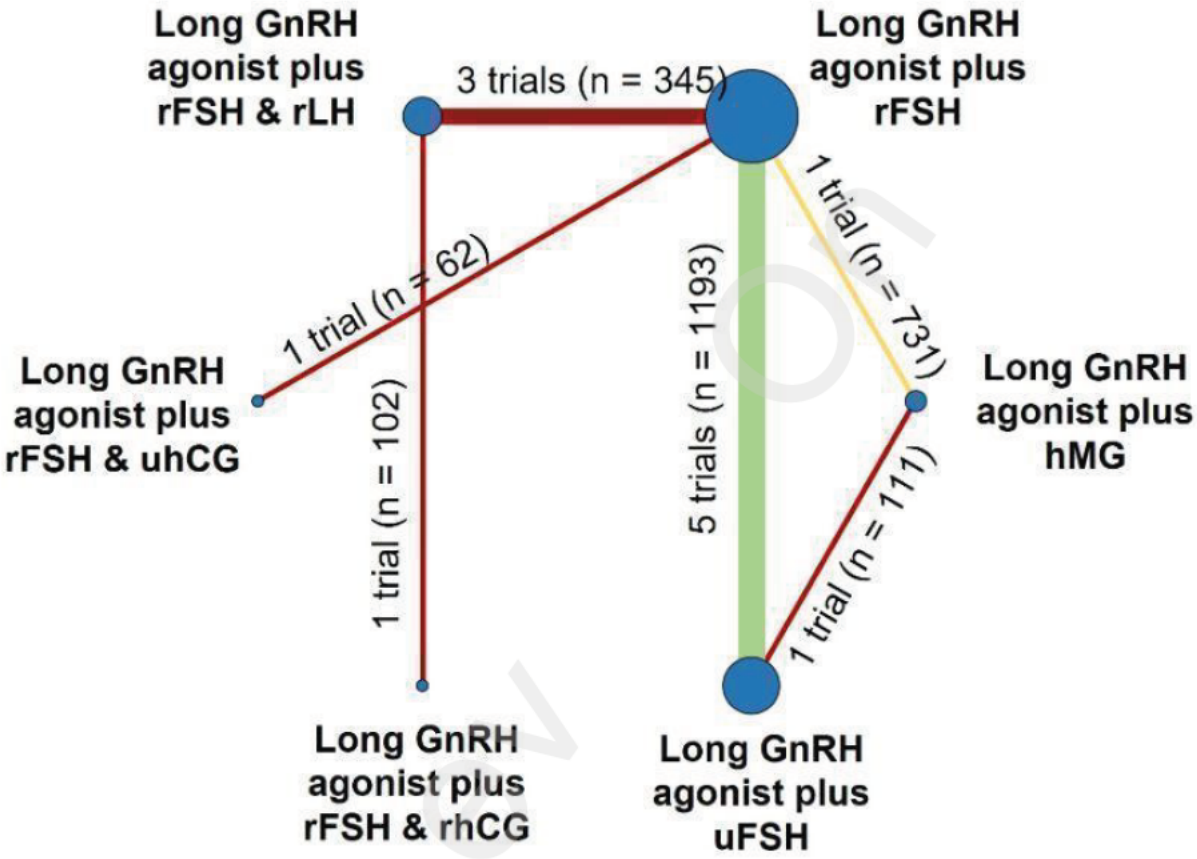


Long GnRH agonist protocols - primary analysis

Figure 6 shows the network diagram for live birth in women with predicted normal response undergoing long GnRH agonist protocols. The network was connected. There were three compar sons for which only direct evidence was available; three comp riso s for which both direct and indirect evidence were available; and nine indirect comparisons evaluated through network meta-analysis.

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Figure 6. Primary analysis: network diagram of long GnRH agonist protocols for the outcome of live birth in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is light green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

rFSH & rLH versus rFSH

The evidence is very uncertain about this comparison (RR 1.05, 95% CI 0.48 to 2.30, 3 studies, 345 women, I^2 = 60%; very low-certainty evidence; Analysis 10.1).

rFSH & rhCG versus rFSH & rLH

The evidence is ve y uncertain about this comparison (RR 1.38, 95% CI 0.60 to 13, study, 102 women; very low-certainty evidence; Analysis 13

rFSH & uhCG versus rFSH

The evidence is very uncertain about this comparison (RR 1.74, 0.22 to 13.79, 1 study, 62 women; very low-certainty evidence; Analysis 14.1).

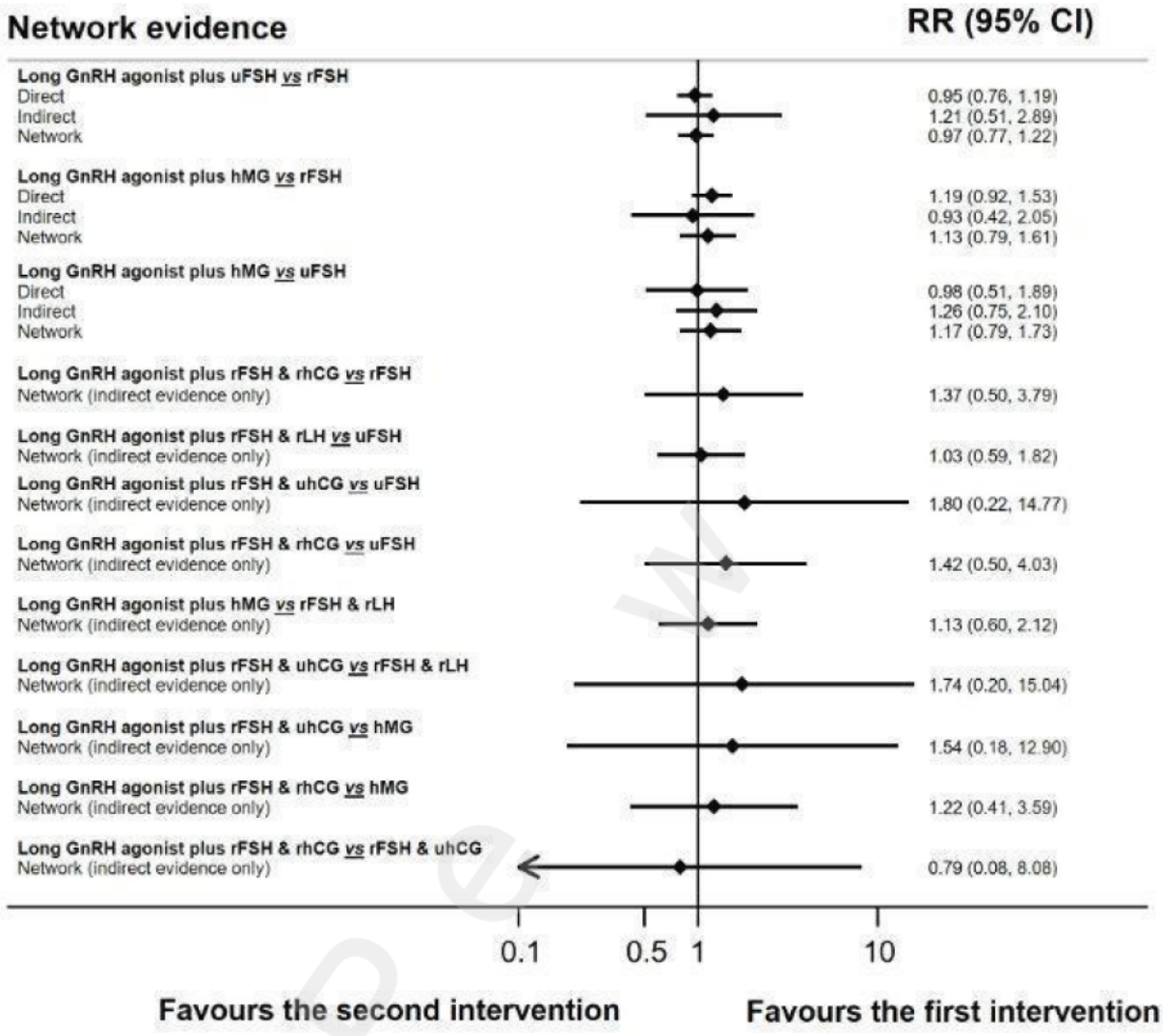
Network estimates

uFSH versus rFSH (direct and indirect evidence)

In women undergoing long GnRH agonist protocols, uFSH probably results in little to no change in live birth versus rFSH (RR 0.97, 95% CI 0.77 to 1.22; moderate-certainty evidence; direct evidence: Analysis 6.1; network evidence: Figure 7).

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Figure 7. Primary analysis: forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (direct, indirect and network estimates; where no RCTs were conducted for a specific comparison, only the indirect [network] estimate is presented) for the outcome of live birth in women with predicted normal response.



hMG versus rFSH (direct and indirec evidence)

The use of hMG may result in little o no difference in live birth versus rFSH (RR 1.13, 95% C 0.79 to 1.61; low-certainty evidence; direct evidence: Analysis 7. network evidence: Figure 7).

hMG versus uFSH (d rect a d indirect evidence)

The network eviden is very uncertain about this comparison (RR 1.17, 95% CI 0.79 to 73; very low-certainty evidence; direct evidence: Analysis 8.1; network evidence: Figure 7).

Remaining network comparisons

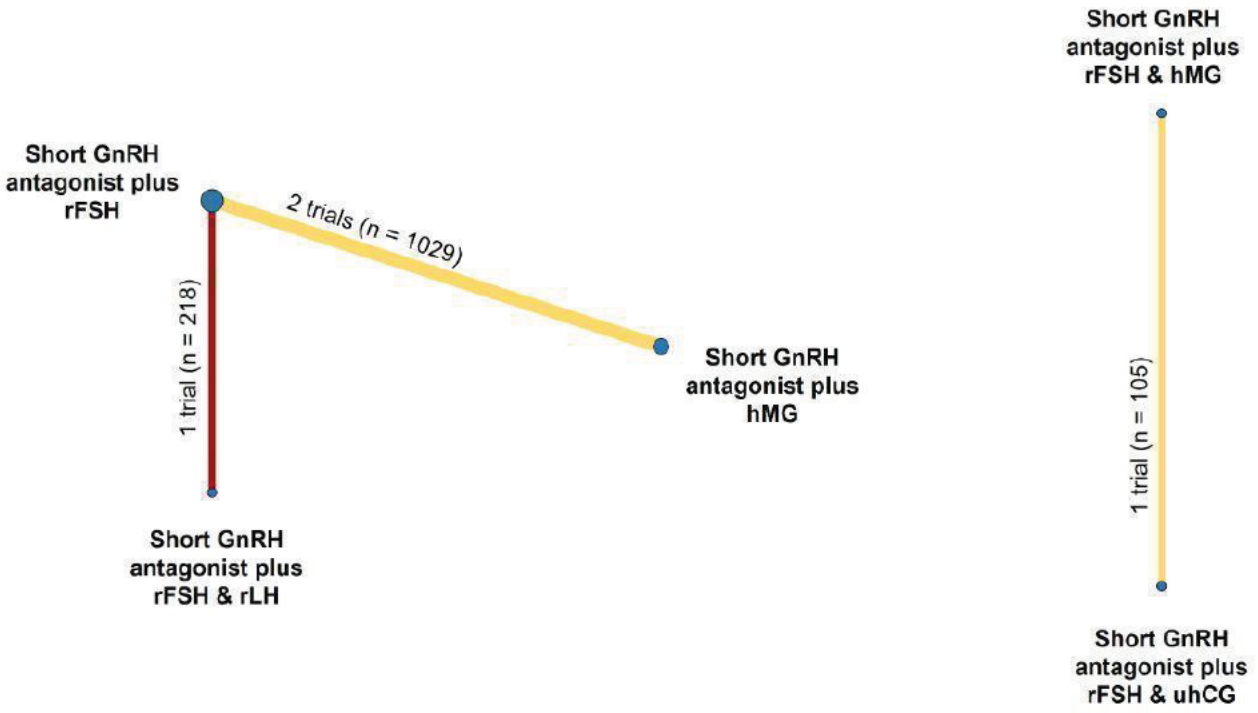
For the nine remaining indirect comparisons, the network evidence was very uncertain (for effect estimates, see Figure 7).

Short GnRH antagonist protocols - primary analysis

Figure 8 shows the network diagram for live birth in women with predicted normal response undergoing short GnRH antagonist protocols. The network was disconnected. There were three direct comparisons and one indirect comparison.

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Figure 8. Primary analysis: network diagram of short GnRH antagonist protocols for the outcome of live birth in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparisons

hMG versus rFSH

Human menopausal gonadotrophin may result in little to no difference in live birth versus rFSH (RR 1.08, 95% CI 1.08 to 1.31, 2 studies, 1029 women, I^2 = 0%; low certainty evidence; Analysis 17.1).

rFSH & rLH versus rFSH

The evidence is very uncertain about this comparison (RR 1.07, 95% CI 0.66 to 1.75, 1 study, 21 women; very low-certainty evidence; Analysis 18.1).

rFSH & uhCG versus rFSH & hMG

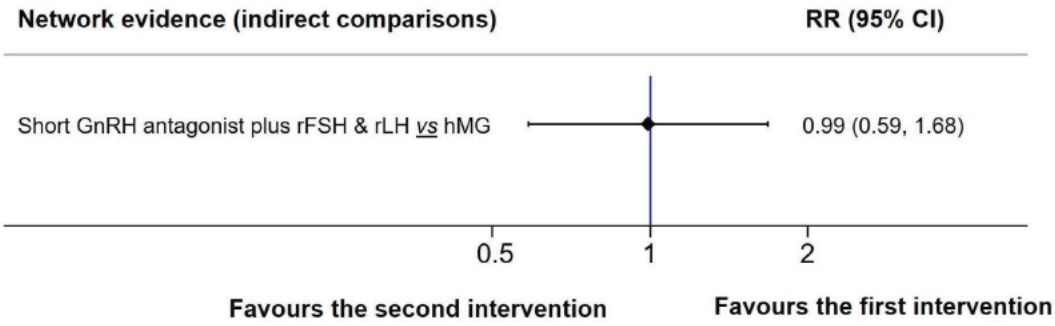
Combined rFSH and uhCG may result in little to no change in live birth versus combined rFSH and hMG (RR 1.22, 95% CI 0.54 to 2.76, 1 study, 105 women; low-certainty evidence; Analysis 23.1).

Network estimates (indirect evidence only)

For the remaining comparison (rFSH & rLH versus hMG), the evidence is very uncertain (RR 0.99, 95% CI 0.59 to 1.68; very low-certainty evidence; Figure 9).

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Figure 9. Primary analysis: forest plot comparing short GnRH antagonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect evidence only) for the outcome of live birth in women with predicted normal response.



Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of live birth in women with predicted normal response.

Sensitivity analysis - predicted normal response (live birth)

Below we provide details of network evidence for which the sensitivity analysis including all studies, irrespective of risk o bias, changed effect estimates and/or the certainty of the primary findings for live birth n women with predicted normal response. For the rema ning tworks sensitivity analyses did not materially change the primary fi dings in this subgroup of women.

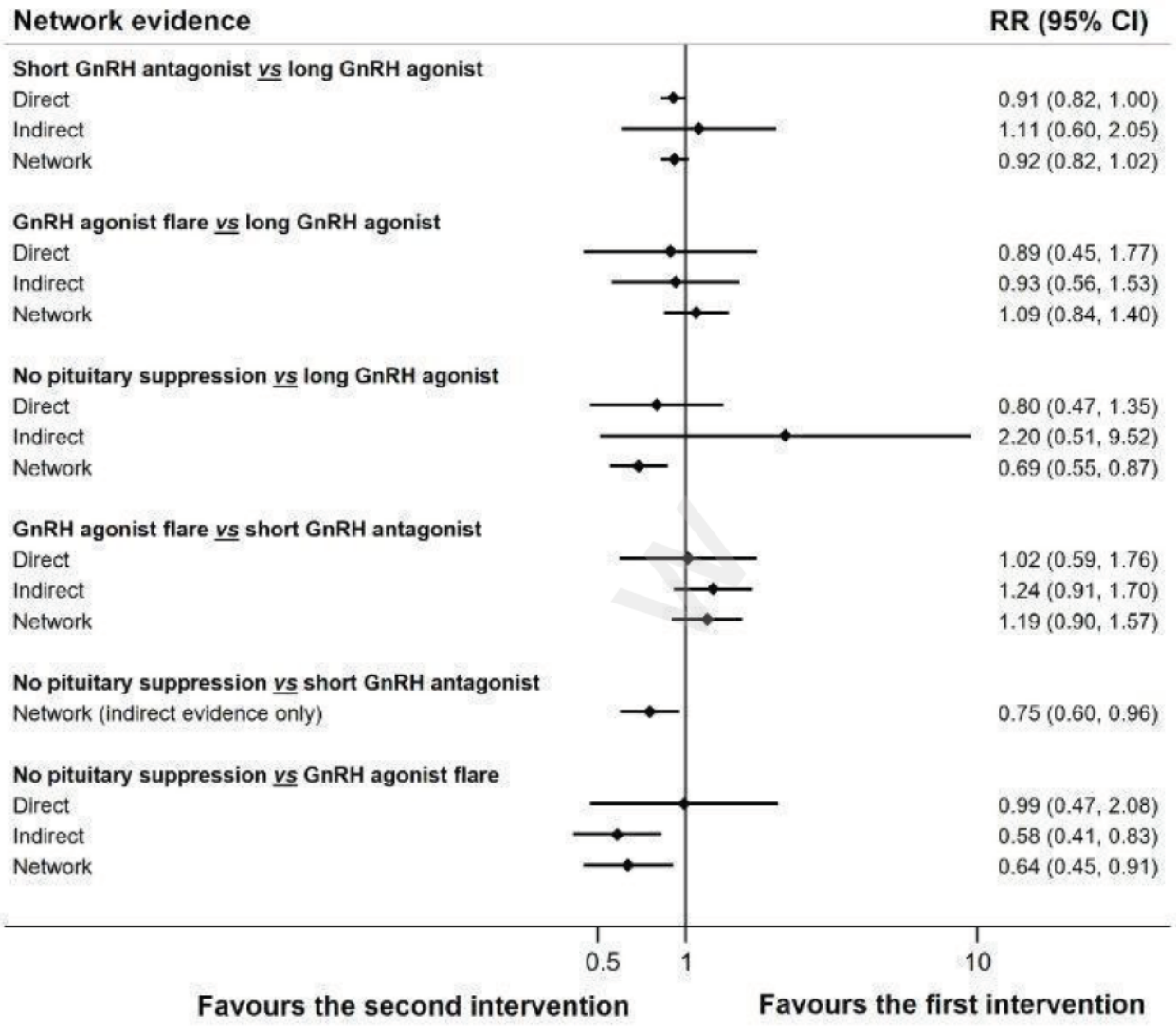
Pituitary su pression methods - sensitivity analysis

No pituitary suppression versus long GnRH agonist (direct and indirect evidence)

Ova ian stimulation without pituitary suppression may reduce live birth ersus long GnRH agonist protocols (RR 0.69, 95% CI 0.55 to 0.87; low-certainty evidence; direct evidence: Analysis 32.1; network evidence: Figure 10).

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Figure 10. Sensitivity analysis: forest plot comparing pituitary suppression methods with relative risk ratios and 95% confidence intervals (CI) from network meta-analysis (direct, indirect and network estimates; where no RCTs were conducted for a specific comparison, only the indirect [network] estimate is presented) for the outcome of live birth in women with predicted normal response.



No pituitary suppression versus short GnRH antagonist (indirect evidence only)

Ovarian stimulation without pituitary suppression may reduce live birth versus short GnRH antagonist protocols (RR 0.75, 95% CI 0.60 to 0.96; low-certainty evidence; Figure 10).

No pituitary suppression versus GnRH agonist flare (direct and indirect evidence)

Ovarian stimulation without pituitary suppression may reduce live birth versus with GnRH agonist flare protocols (RR 0.64, 95% CI 0.45 to 0.91; low-certainty evidence; direct evidence: Analysis 33.1; network evidence: Figure 10).

Long GnRH agonist protocols - sensitivity analysis

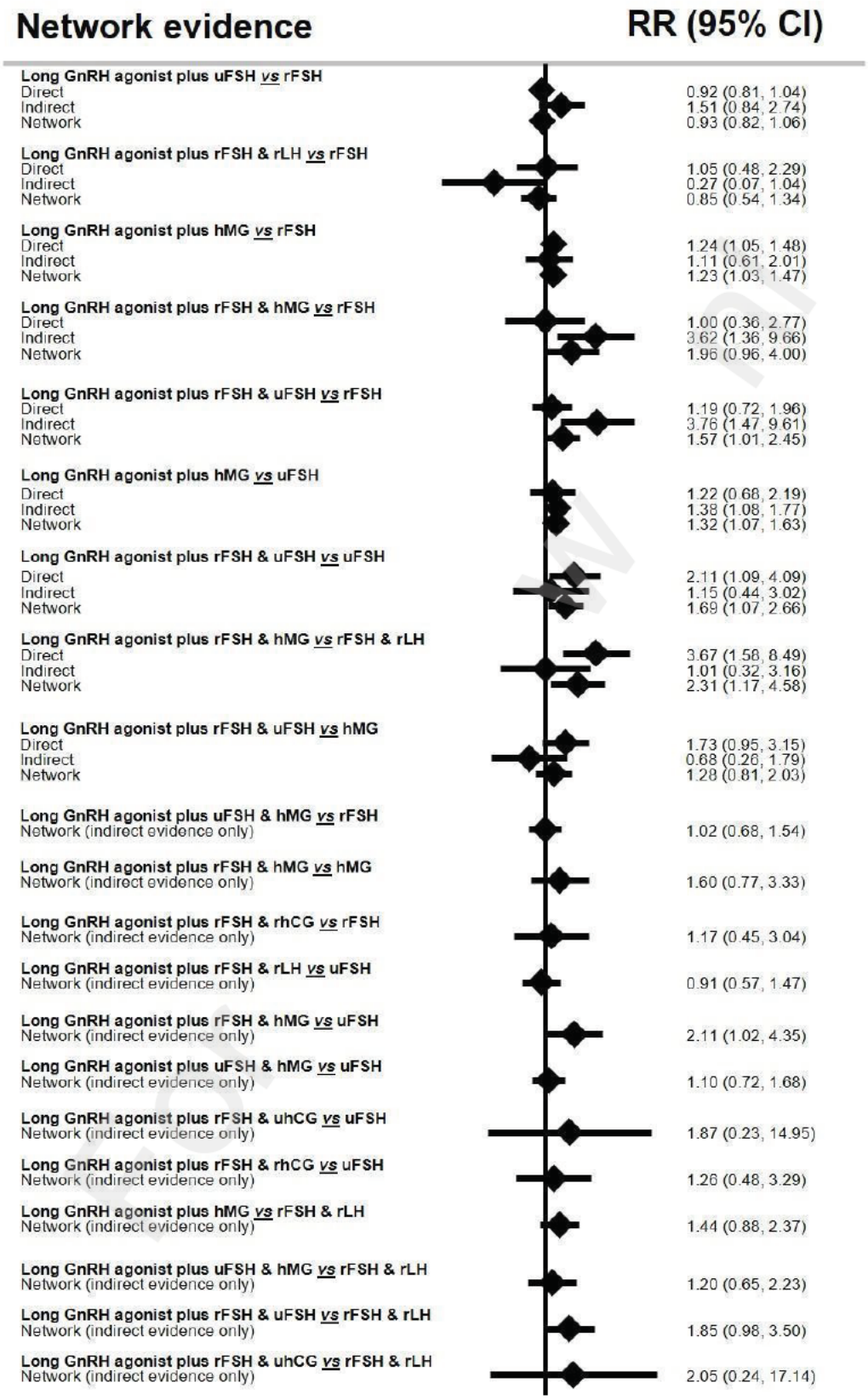
hMG versus rFSH (direct and indirect evidence)

Network estimates obtained from the sensitivity analysis including all studies show that hMG probably increases live birth in comparison to rFSH (RR 1.23, 95% CI 1.03 to 1.47; moderate-certainty evidence; direct evidence: Analysis 34.1; network evidence: Figure 11).

Figure 11. Sensitivity analysis: forest plot comparing long GnRH agonist protocols with relative risk ratios and 95% confidence intervals (CI) from network meta-analysis (direct, indirect and network estimates; where no RCTs were

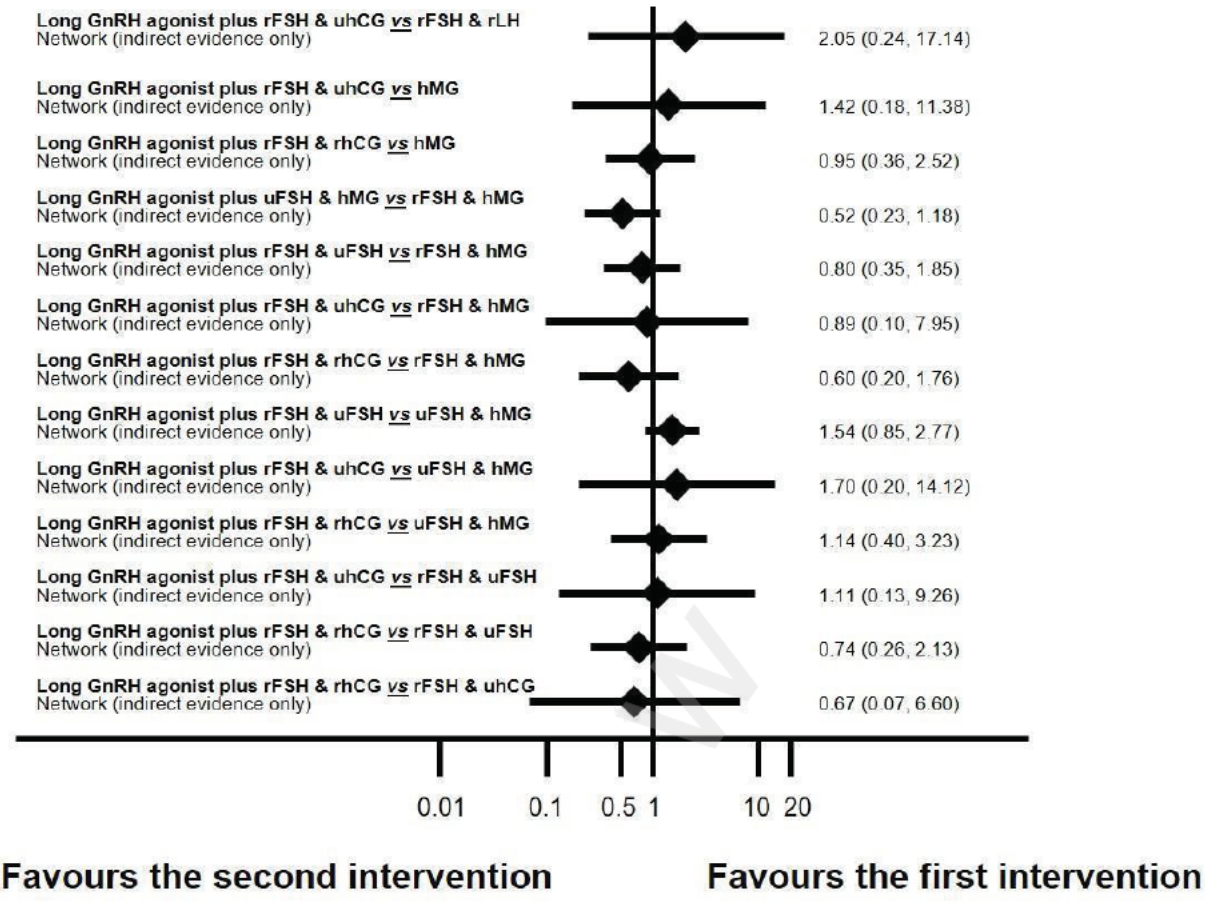
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conducted for a specific comparison, only the indirect [network] estimate is presented) for the outcome of live birth in women with predicted normal response.



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Figure 11. (Continued)



rFSH & uFSH versus rFSH (direct and indirect evidence

For this comparison, no studies reporting live bir in women with predicted normal response were found to ave a low risk of selection and other biases. Network est mat s from the sensitivity analysis including all studies suggest that rFSH & uFSH may improve live birth versus rFSH (RR 1 57, 95% CI 1.01 to 2.45; low-certainty evidence; direct evidence: Analysis 37.1; network evidence: Figure 11).

hMG versus uFSH (direct and indirect evidence)

Network estimates obtained from the sensitivity analysis including all studies show that hMG prob bly improves live birth in comparison to uFSH (RR 1 2, 95% CI 1.07 to 1.63; moderate-certainty evidenc ; direct evidence: Analysis 35.1; network evidence: Figure 1)

rFSH & uFSH versus uFSH (direct and indirect evidence)

For this comparison, no studies reporting live birth in women with predicted normal response were found to have a low risk of selection and other biases. Network estimates from the sensitivity analysis including all studies suggest that rFSH & uFSH may improve live birth versus uFSH (RR 1.69, 95% CI 1.07 to 2.66; low-certainty evidence; direct evidence: Analysis 38.1; network evidence: Figure 11).

rFSH & hMG versus rFSH & rLH (direct and indirect evidence)

Combined rFSH and hMG may improve live birth versus combined rFSH and rLH (RR 2.31, 95% CI 1.17 to 4.58; low-certainty evidence; direct evidence: Analysis 40.1; network evidence: Figure 11).

1.2. Women with predicted HIGH response

Pituitary suppression methods – primary analysis

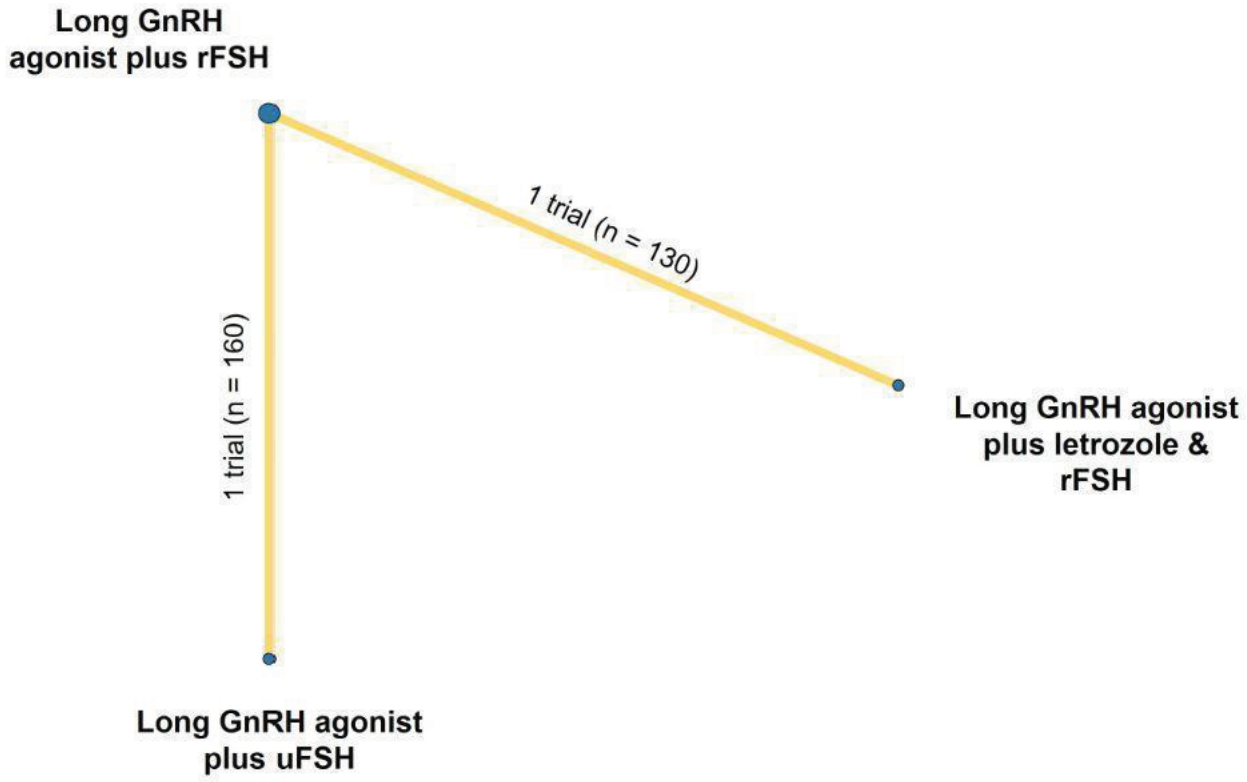
The searches did not identify any studies at low risk of selection and other biases comparing different pituitary suppression protocols in women with predicted high response.

Long GnRH agonist protocols – primary analysis

Figure 12 shows the network diagram for live birth in women with predicted high response undergoing long GnRH agonist protocols. The network was connected. There were two direct comparisons and one indirect comparison.

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Figure 12. Primary analysis: network diagram of long GnRH agonist protocols for the outcome of live birth in women with predicted high response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence.



Direct comparisons

uFSH versus rFSH

Urinary FSH may result in little to no difference in live birth versus rFSH (RR 1.12, 95% CI 0.63 to 1.99, 1 study, 160 women; low-certainty evidence; Analysis 6.1).

rFSH & letrozole versus rFSH

Combined rFSH and letrozole may result in little to no change in live birth versus rFSH (RR 0.70, 95% CI 0.45 to 1.09, 1 study, 130 women; low-certainty evidence; Analysis 9.1).

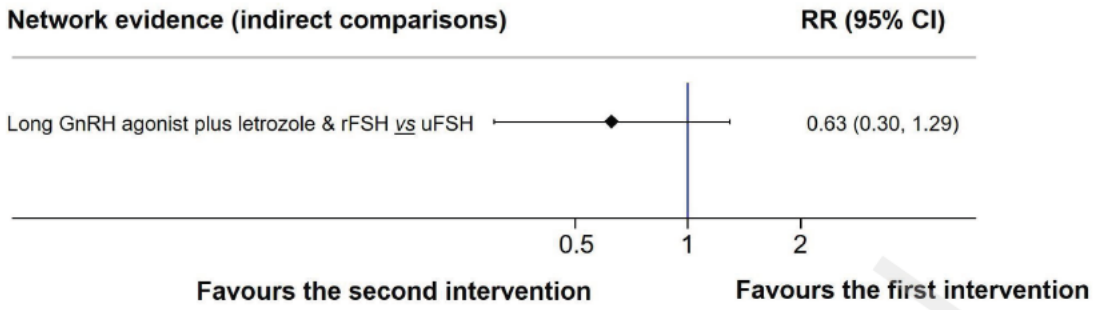
Network estimates (indirect evidence only)

Letrozole & rFSH versus uFSH

Combined rFSH and letrozole may result in little to no change in live birth versus uFSH (RR 0.63, 95% CI 0.30 to 1.29; low-certainty evidence; Figure 13).

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Figure 13. Primary analysis: forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect evidence only) for the outcome of live birth in women with predicted high response.



Short GnRH antagonist protocols - primary analysis

There was only one comparison for live birth in women with predicted high response undergoing short GnRH antagonist protocols (hMG versus rFSH).

hMG versus rFSH

Human menopausal gonadotrophin may result in little to no change in live birth versus rFSH (RR 1.13, 95% CI 0.89 to 1.42, 1 study, 619 women; low-certainty evidence; Analysis 17.1).

Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of live birth in women with predicted high response.

Sensitivity analysis - predicted high response (live birth)

The sensitivity analysis did not materially change the primary findings in this subgroup of women.

1.3. Women with predicted LOW response

Pituitary suppression methods – primary analysis

The searches did not identify any studies at low risk of selection and other biases comparing different pituitary suppression protocols in women with predicted low response for the outcome of live birth.

Long GnRH agonist protocols - primary analysis

There was only one direct comparison for live birth in women with predicted low response undergoing long GnRH agonist protocols (rFSH & rLH versus rFSH).

rFSH & rLH versus rFSH

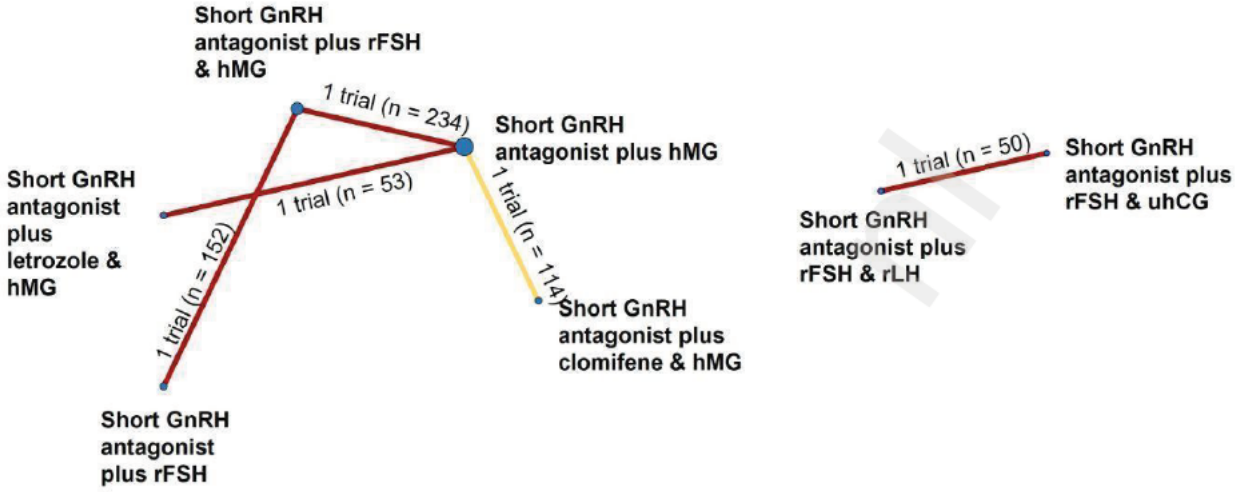
Combined rFSH and rLH may result in little to no difference in live birth versus rFSH (RR 0.90, 95% CI 0.63 to 1.30, 1 study, 939 women; low-certainty evidence; Analysis 10.1).

Short GnRH antagonist protocols - primary analysis

Figure 14 presents the network diagram for live birth in women with predicted low response undergoing short GnRH antagonist protocols. The network was disconnected. There were five direct comparisons and six indirect comparisons.

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Figure 14. Primary analysis: network diagram of short GnRH antagonist protocols for the outcome of live birth in women with predicted low response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparisons

rFSH & hMG versus rFSH

Combined rFSH and hMG may result in little to no difference in live birth versus rFSH (RR 0.97, 95% CI 0.43 to 2.20, 1 study, 15 women; low-certainty evidence; Analysis 19.1).

rFSH & hMG versus hMG

The evidence is very uncertain about this comparison (RR 0.77, 95% CI 0.43 to 1.38, 1 study, 234 w m ; ve y low-certainty evidence; Analysis 20.1).

rFSH & uhCG versus rFSH & rLH

The evidence is very uncertain about this comparison (RR 2.00, 95% CI 0.19 to 20.67, 1 study, 50 women; very low-certainty evidence; Analysis 22.1).

Clomifene & hMG versus hMG

ombined clomifene and hMG may result in little to no difference in live birth versus hMG (RR 0.60, 95% CI 0.15 to 2.39, 1 study, 114 women; low-certainty evidence; Analysis 24.1).

Letrozole & hMG versus hMG

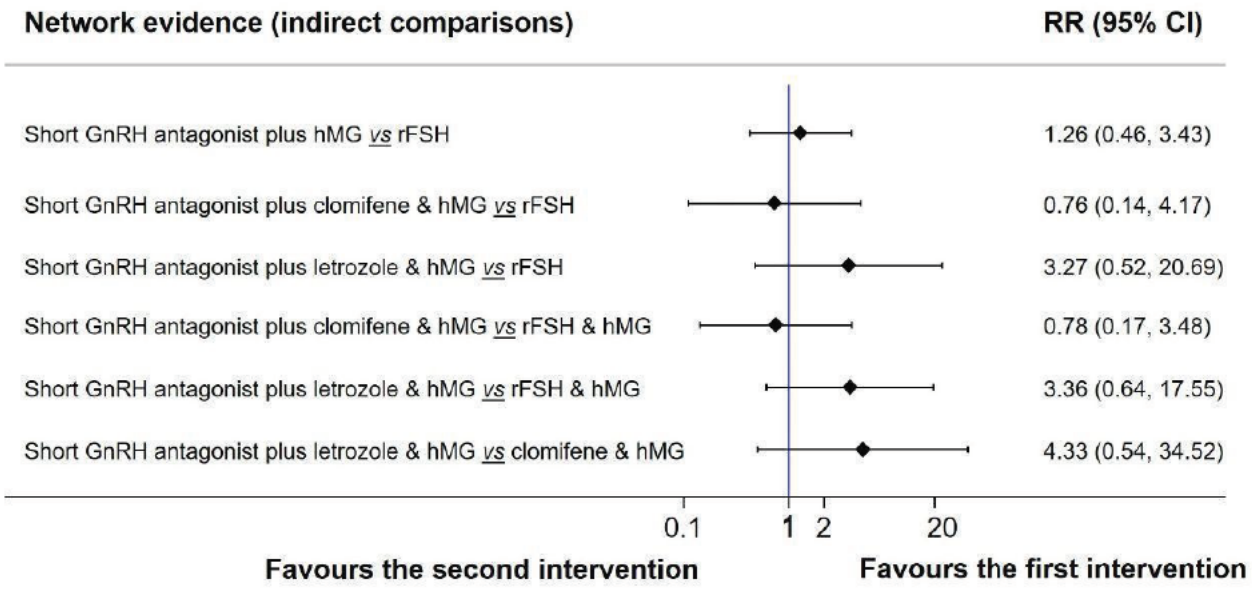
The evidence is very uncertain about this comparison (RR 2.60, 95% CI 0.55 to 12.22, 1 study, 53 women; very low-certainty evidence; Analysis 25.1).

Network estimates (indirect evidence only)

For the six remaining indirect comparisons, the network evidence is very uncertain (for effect estimates, see Figure 15).

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Figure 15. Primary analysis: forest plot comparing short GnRH antagonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of live birth in women with predicted low response.



Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of live bir in women with predicted low response.

Sensitivity analysis - predicted low response (live birth)

The sensitivity analysis did not materially change the primary findings in this subgroup of women.

2. Ovarian hyperstimulation syndrome

2.1. Women with predicted NORMAL r sponse

Pituitary suppression methods – primary analysis

There was only one comparison o pituitary suppression methods for the outcome of OHSS in women with predicted normal response (short GnRH antagonist versus long GnRH agonist).

Short GnRH antagonist versus long GnRH agonist

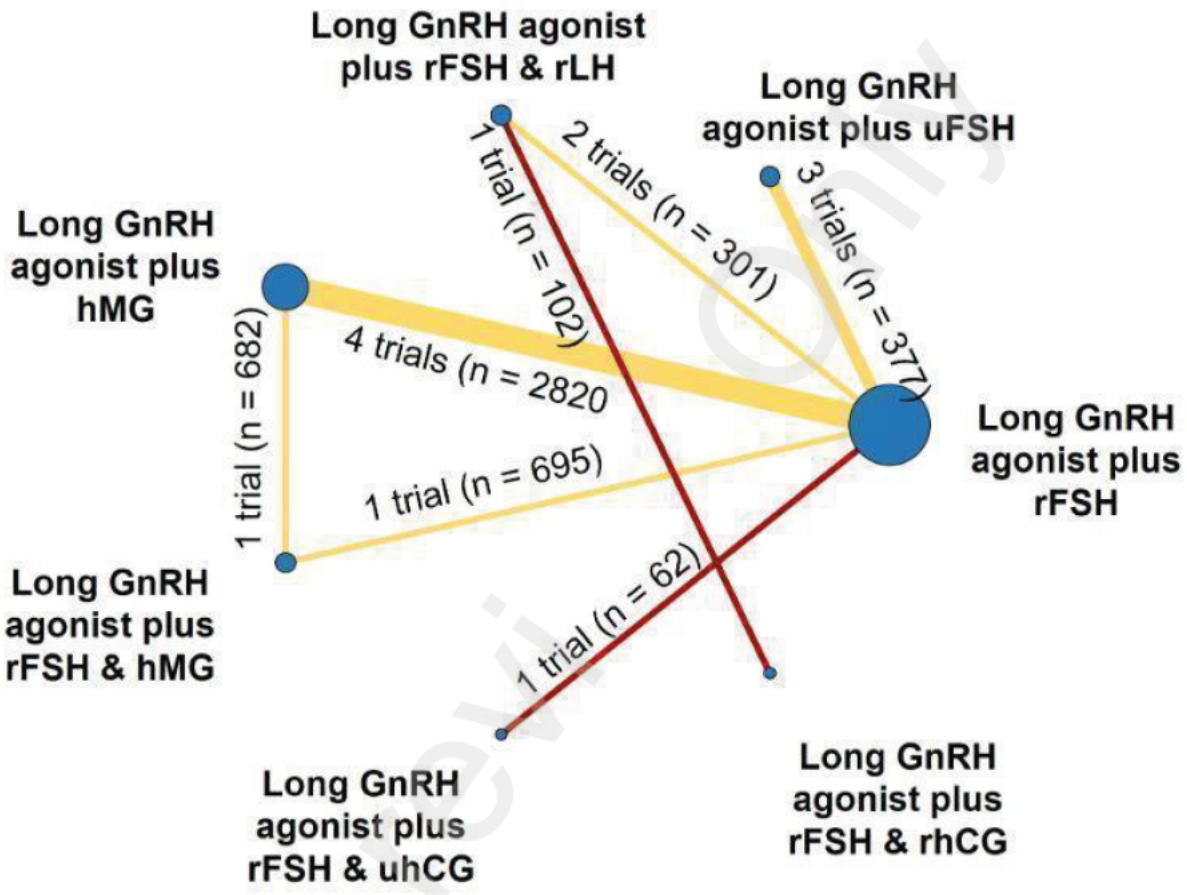
Short antagonist protocols probably reduce OHSS versus long ago ist protocols (RR 0.88, 95% CI 0.78 to 0.99, 5 studies, 1890, I^2 = 0% moderate-certainty evidence; Analysis 1.2).

Long GnRH agonist protocols - primary analysis

Figure 16 presents the network diagram for OHSS in women with predicted normal response undergoing long GnRH agonist protocols. The network was connected. There were four comparisons for which only direct evidence was available; three comparisons for which both direct and indirect evidence were available; and fourteen indirect comparisons evaluated through network meta-analysis.

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Figure 16. Primary analysis: network diagram of long GnRH agonist protocols for the outcome of OHSS in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



For review only

Direct comparisons

uFSH versus rFSH

Urinary FSH may result in little to no difference in OHSS versus rFSH (RR 0.82, 95% CI 0.32 to 2.1 , 3 stu ies, 377 women, I^2 = 0%; low-certainty evidence; A alysis 6 2).

rFSH & rLH versus FSH

Combined rFSH and rL may result in little to no difference in OHSS versus rFSH (RR 0.15, 95% C 0.01 to 2.90, 2 studies, 301 women; low-certainty evidence; Analysis 10.2).

rFSH & rhCG versus rFSH & rLH

The evidence is very uncertain about this comparison (RR 0.20, 95% CI 0.01 to 4.07, 1 study, 102 women; very low-certainty evidence; Analysis 13.2).

rFSH & uhCG versus rFSH

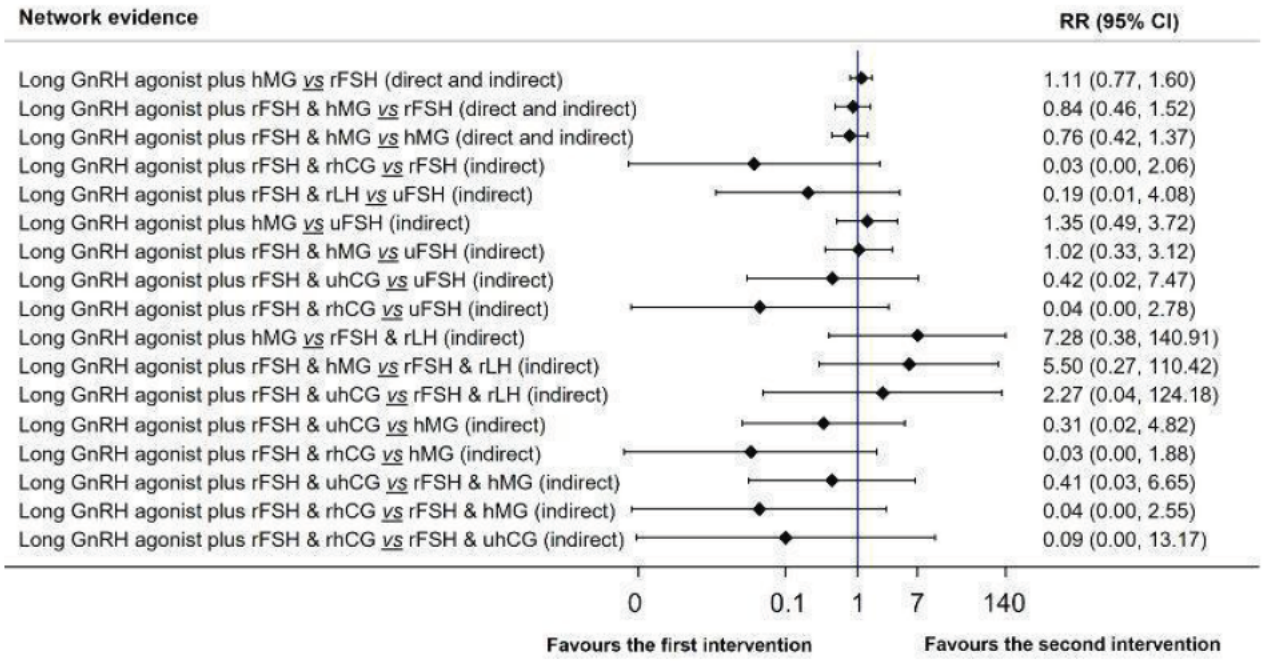
The evidence is very uncertain about this comparison (RR 0.35, 95% CI 0.02 to 5.24, 1 study, 62 women; very low-certainty evidence; Analysis 14.2).

Network estimates

For the seventeen remaining comparisons, the network evidence is either uncertain or very uncertain (for effect estimates, see Figure 17).

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Figure 17. Primary analysis: forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (network estimates from combined direct and indirect evidence; where no RCTs were conducted for a specific comparison, only the indirect estimate is presented) for the outcome of OHSS in women with predicted normal response.

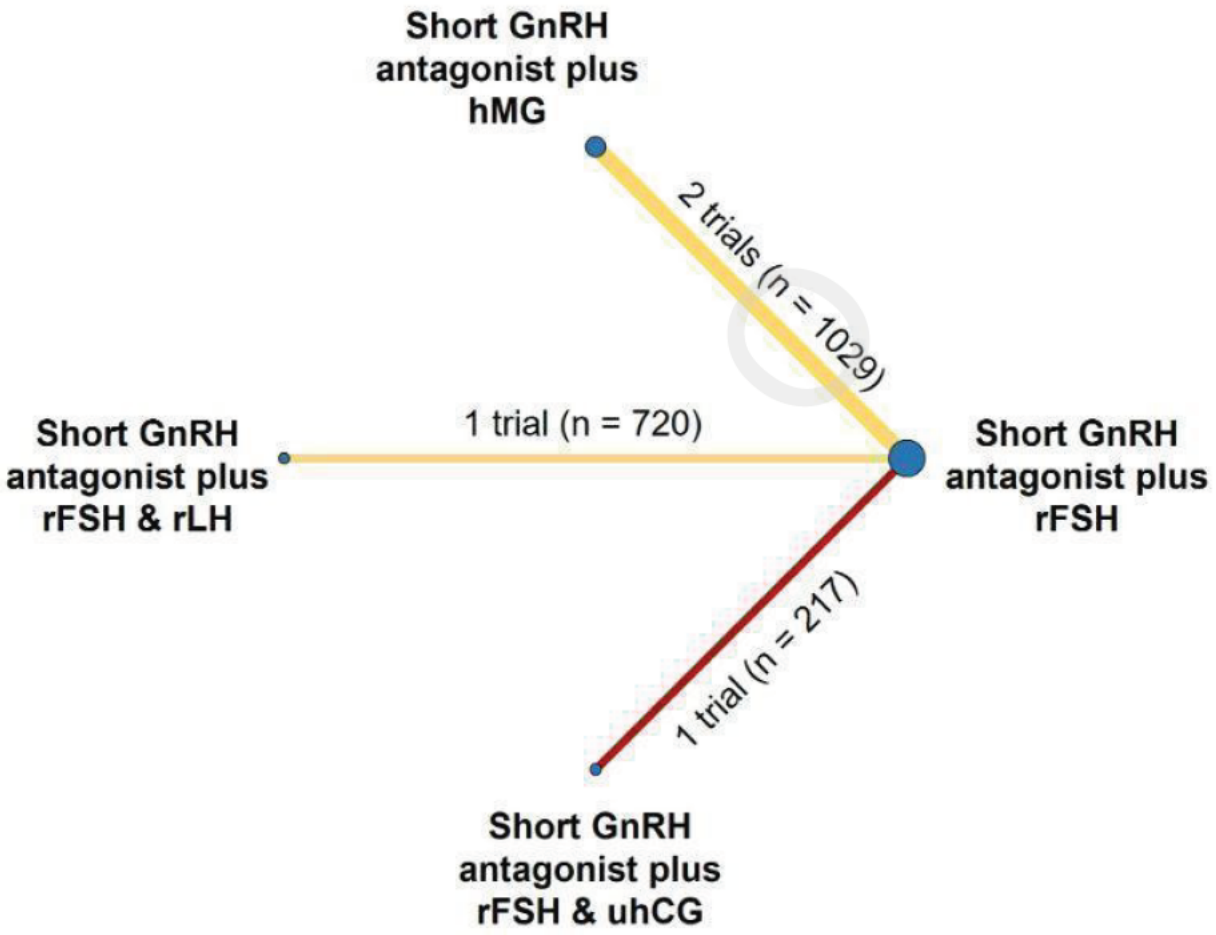


Short GnRH antagonist protocols - primary analysis

Figure 18 presents the network diag m for OHSS in women with predicted normal response undergoing hort GnRH antagonist protocols. The network was connected. There were three direct comparisons and three indirect comparisons.

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Figure 18. Primary analysis: network diagram of short GnRH antagonist protocols for the outcome of OHSS in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

hMG versus rFSH

Human menopausal gonadotrophin may result in little to no difference in OHSS versus FSH (RR 1.26, 95% CI 0.65 to 2.48, 2 studies, 1029 wome , I^2 = 0%; low-certainty evidence; Analysis 17.2).

rFSH & rLH versus rF H

Combined rFSH and rLH may result in little to no difference in OHSS versus rFSH (RR 0.80, 95% CI 0.22 to 2.96, 1 study, 720 women; low-certainty evidence; Analysis 18.2).

rFSH & uhCG versus rFSH

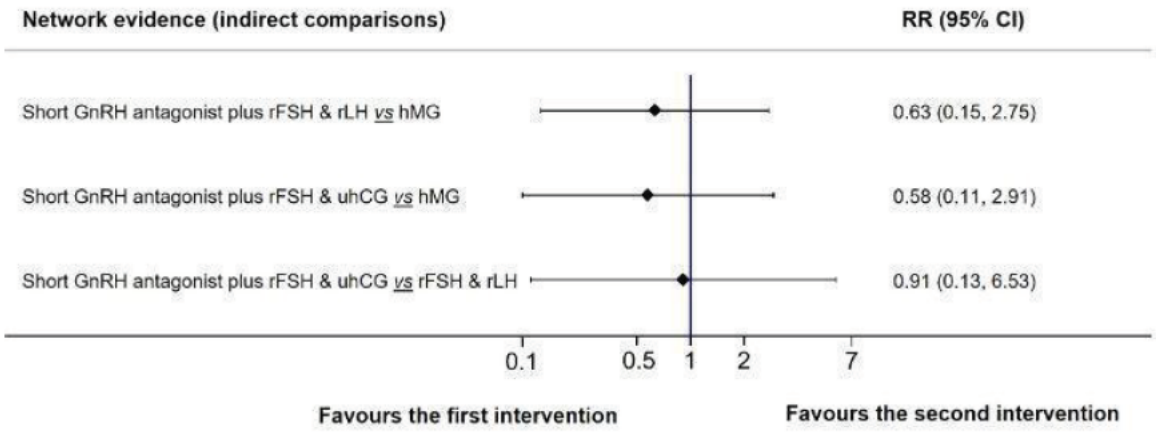
The evidence is very uncertain about this comparison (RR 0.73, 95% CI 0.17 to 3.18, 1 study, 217 women; very low-certainty evidence; Analysis 21.1).

Network estimates (indirect evidence only)

For the three remaining comparisons, the network evidence is either uncertain or very uncertain (for effect estimates, see Figure 19).

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Figure 19. Primary analysis: forest plot comparing short GnRH antagonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect estimates only) for the outcome of OHSS in women with predicted normal response.



Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulat n wit out pituitary suppression

The primary analysis did not include ny studies comparing interventions within these networks for the outcome of OHSS in women with predicted normal response.

Sensitivity analysis - predic ed normal response (OHSS)

Below we provide details of network evidence for which the sensitivity analys including all studies, irrespective of risk of bias, changed effe t est mates and/or the certainty of the primary findings for OHSS in w men with predicted normal response. For the remaining networks, ensitivity analyses did not materially change the primary findings.

Pituitary suppression methods – sensitivity analysis

No pituitary suppression versus long GnRH agonist (direct evidence only)

For this comparison, no studies reporting OHSS in women with predicted normal response were found to have a low risk of selection and other biases. The sensitivity analysis including all studies shows that protocols using no pituitary suppression may reduce OHSS versus long GnRH agonist protocols (RR 0.30, 95% CI 0.10 to 0.92, 1 study, 294 women; low-certainty evidence; Analysis 32.2).

Long GnRH agonist protocols - sensitivity analysis

rFSH & rLH versus rFSH (direct evidence only)

Long GnRH agonist protocols with rFSH and rLH probably reduce OHSS versus long GnRH agonist with rFSH (RR 0.16, 95% CI 0.03 to 0.90, 4 studies, 1420 women, I^2 = 0%; moderate-certainty evidence; Analysis 36.2).

2.2. Women with predicted HIGH response

Pituitary suppression methods – primary analysis

There was only one comparison of pituitary suppression methods for the outcome of OHSS in women with predicted high response.

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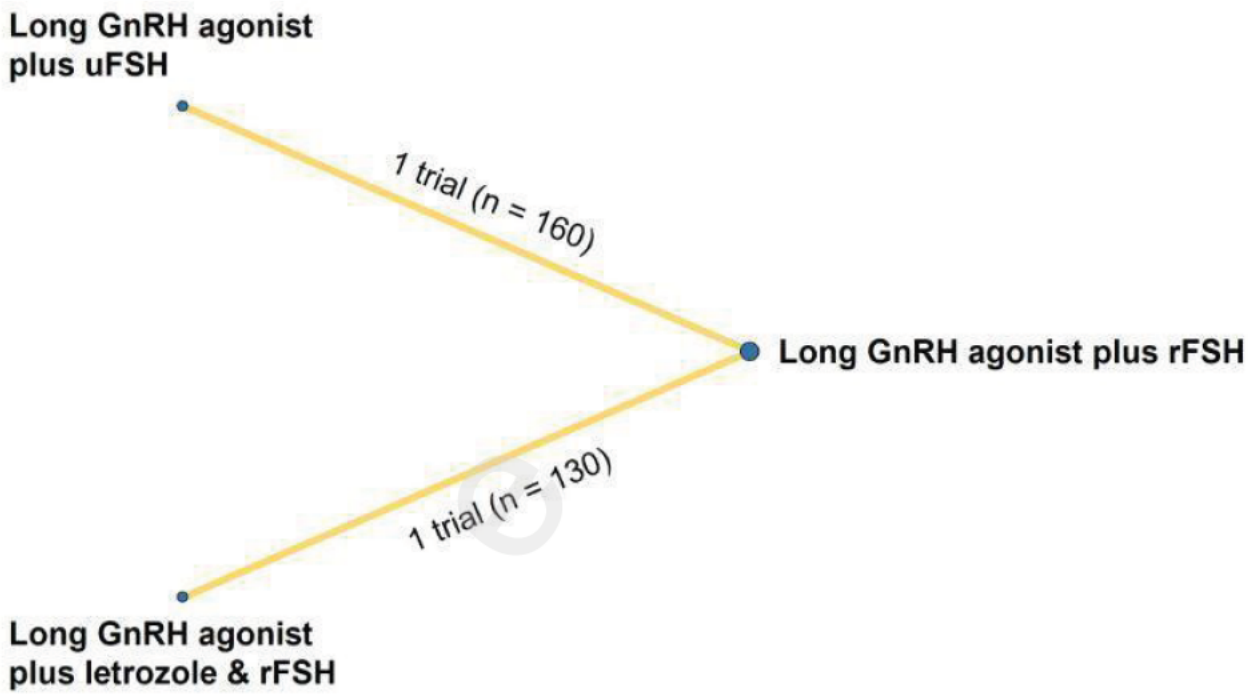
Short GnRH antagonist versus long GnRH agonist

Short antagonist protocols may result in little to no difference to OHSS versus long agonist protocols (RR 0.89, 95% CI 0.33 to 2.41, 2 studies, 356 women, I^2 = 0%; low-certainty evidence; Analysis 1.2).

Long GnRH agonist protocols - primary analysis

Figure 20 presents the network diagram for OHSS in women with predicted high response undergoing long GnRH agonist protocols. The network was connected. There were two direct comparisons and one indirect comparison.

Figure 20. Primary analysis: network diagram of long GnRH agonist protocols for the outcome of OHSS in women with predicted high response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is am er for low-certainty evidence.



Direct comparisons

uFSH versus rFSH

Urinary FSH may result in li tle to no difference in OHSS versus rFSH (RR 1.17, 95% CI 0.41 to 3.32, 1 study, 160 women; low-certainty evidence; Analysis 6.2).

Letrozole & rFSH versus rFSH

Combined letrozole and rFSH may result in little to no difference in OHSS versus using rFSH (RR 0.33, 95% CI 0.01 to 8.03, 1 study, 130 women; low-certainty evidence; Analysis 9.2).

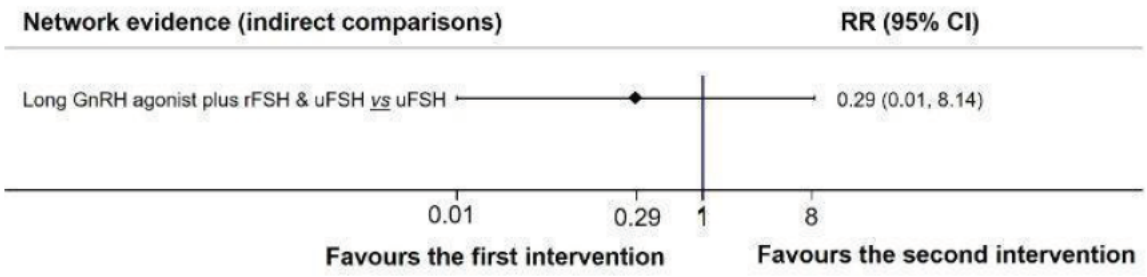
Network estimates (indirect evidence only)

rFSH & uFSH versus uFSH

Combined rFSH and uFSH may result in little to no difference in OHSS versus uFSH (RR 0.29, 95% CI 0.01 to 8.14; low-certainty evidence; Figure 21).

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Figure 21. Primary analysis: forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of OHSS in women with predicted high response.



Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of OHSS in women with predicted high response.

Sensitivity analysis - predicted high response (OHSS)

Below we provide details of network evidence for which the sensitivity analysis including all studies, irrespective of risk of bias, changed effect estimates and/or the certainty of the primary findings for OHSS in women with predicted high response. For the remaining networks, sensitivity analyses did not materially change the primary findings.

Pituitary suppression methods – sensitivity analysis

Short GnRH antagonist versus long GnRH agonist

The sensitivity analysis including all studies shows that short GnRH antagonist protocols probably result in a large reduction in OHSSs versus long GnRH agonist protocols in this subgroup of women (RR 0.61, 95% CI 0.48 to 0.78, 10 studies, 1878 women, I^2 = 15%; moderate-certainty evidence; Analysis 31.2).

Pituitary suppression methods – sensitivity analysis

Short GnRH antagonist plus letrozole, hMG & rFSH versus short GnRH antagonist plus hMG & rFSH

For this comparison, no studies reporting OHSS in women with predicted high response were found to have a low risk of selection and other biases. The sensitivity analysis including all studies shows that in women with predicted high response undergoing long GnRH agonist protocols, combined letrozole, hMG and rFSH may result in a large reduction OHSS versus combined hMG and rFSH (RR 0.22, 95% CI 0.05 to 0.92, 1 study, 48 women; low-certainty evidence; Analysis 39.2).

2.3. Women with predicted LOW response

The primary and sensitivity analyses included no studies investigating OHSS in women with predicted low response.

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Secondary outcomes

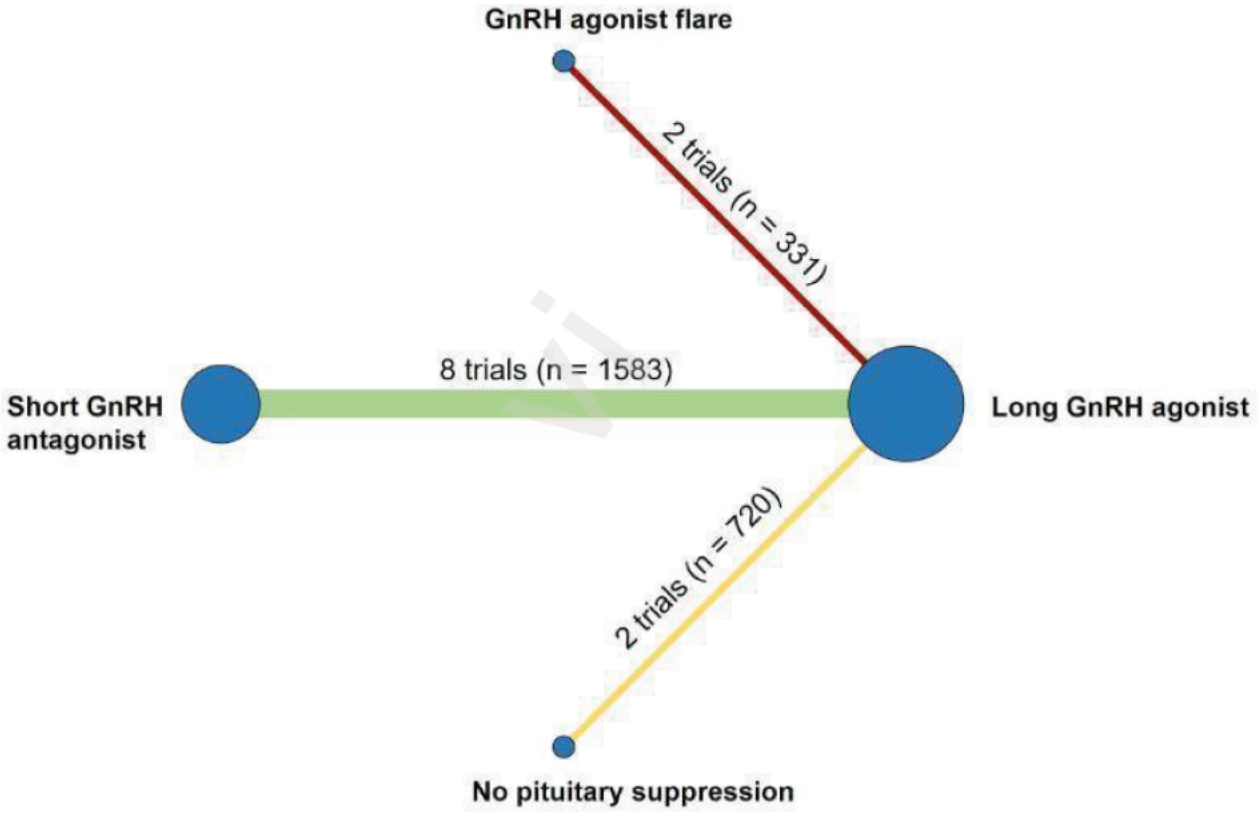
3. Clinical pregnancy

3.1. Women with predicted NORMAL response

Pituitary suppression methods

Figure 22 shows the primary network diagram of pituitary suppression methods for the outcome of clinical pregnancy in women with predicted normal response. The network was connected. There were three direct comparisons and three indirect comparisons.

Figure 22. Network diagram of pituitary suppression methods for the outcome of clinical pregnancy in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting ea h pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent th number f trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evi enc



Direct comparisons

Short GnRH antagonist versus long GnRH agonist

Short antagonist protocols probably result in little to no difference in clinical pregnancy versus long agonist protocols (RR 0.88, 95% CI 0.76 to 1.02, 8 studies, 1583 women, I^2 = 3%; moderate-certainty evidence; Analysis 1.3).

GnRH agonist flare versus long GnRH agonist

The evidence is very uncertain about this comparison (RR 0.85, 95% CI 0.35 to 2.08, 2 studies, 331 women, I^2 = 64%; very low-certainty evidence; Analysis 2.2).

No pituitary suppression versus long GnRH agonist

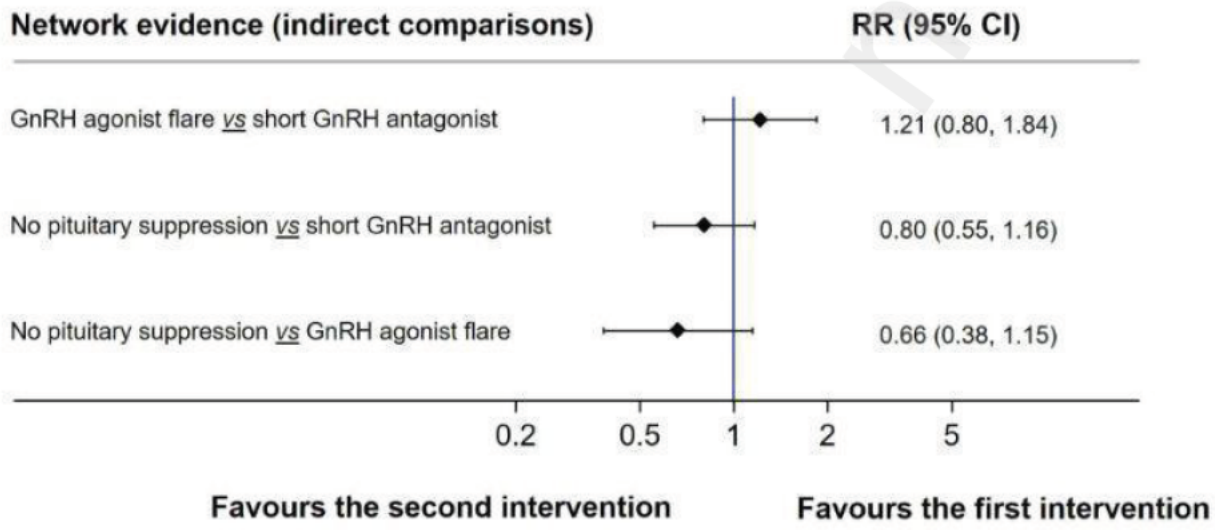
The evidence is very uncertain about this comparison (RR 0.77, 95% CI 0.49 to 1.21, 2 studies, 720 women, I^2 = 68%; very low-certainty evidence; Analysis 3.2).

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Network estimates (indirect estimates only)

For the three remaining comparisons, the network evidence is either uncertain or very uncertain (for effect estimates, see Figure 23).

Figure 23. Forest plot comparing pituitary suppression methods with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of clinical pregnancy in women with predicted normal response.

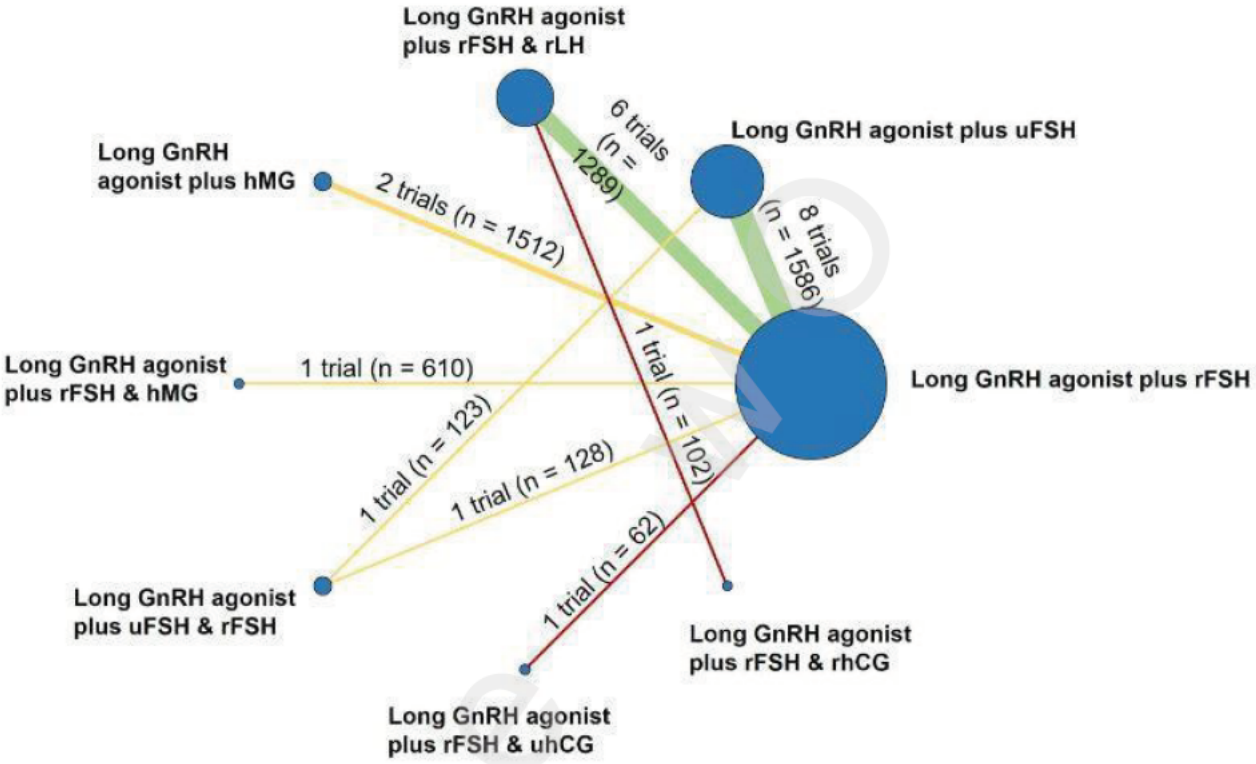


Long GnRH agonist protocols

Figure 24 presents the network diagram for clinical pregnancy in women with predicted normal response undergoing long GnRH agonist protocols. The network wa connected. There were five comparisons for which only direct evidence was available; three comparisons for which both direct and indirect evidence were available; and twenty indirect comparisons evaluated through network meta-analysis.

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Figure 24. Network diagram of long GnRH agonist protocols for the outcome of clinical pregnancy in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

hMG versus rFSH

Human menopausal gonadotrophin may result in little to no difference in clinical pregnancy v rsus rFSH (RR 1.19, 95% CI 0.99 to 1.43, 2 stu ies, 1 12 women, I^2 = 0%; low-certainty evidence; Analysis 7.3).

rFSH & rLH versus rF H

Combined rFSH and rLH p obably results in little to no difference in clinical pregnancy versus rFSH (RR 0.94, 95% CI 0.78 to 1.13, 6 studies, 1289 women, I^2 = 9%; moderate-certainty evidence; Analysis 10.3).

rFSH & rhCG versus rFSH & rLH

The evidence is very uncertain about this comparison (RR 1.18, 95% CI 0.59 to 2.39, 1 study, 102 women; very low-certainty evidence; Analysis 13.3).

rFSH & uhCG versus rFSH

The evidence is very uncertain about this comparison (RR 1.22, 95% CI 0.47 to 3.16, 1 study, 62 women; very low-certainty evidence; Analysis 14.3).

rFSH & hMG versus rFSH

Combined hMG and rFSH may result in little to no difference in clinical pregnancy versus rFSH (RR 1.22, 95% CI 0.93 to 1.59, 1 study, 610 women; low-certainty evidence; Analysis 15.2).

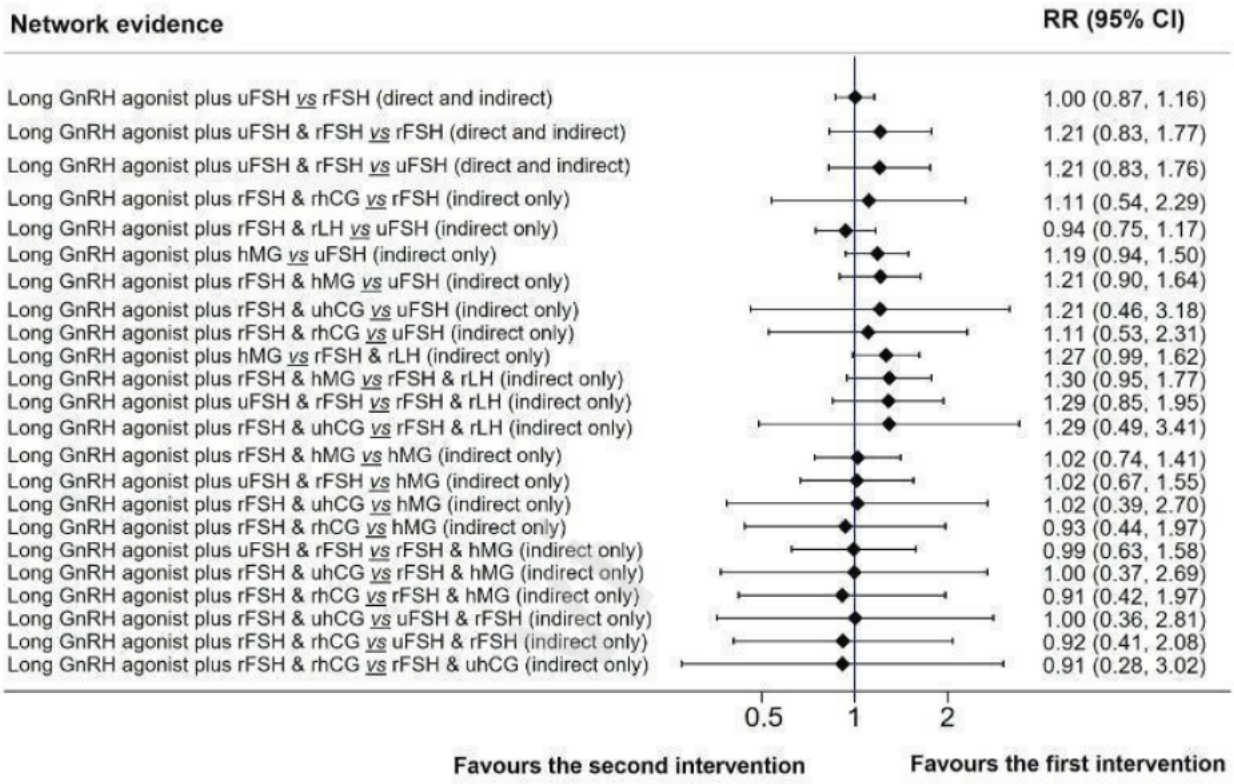
Network estimates

uFSH versus rFSH (direct and indirect evidence)

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Network estimates show that uFSH probably results in little to no difference in clinical pregnancy versus rFSH (RR 1.00, 95% CI 0.87 to 1.16; moderate-certainty evidence; Figure 25).

Figure 25. Forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (network estimates combining direct and indirect evidence; where no RCTs were conducted for a specific comparison, only the indirect estimate is presented) for the outcome of clinical pregnancy in women with predicted normal response.



uFSH & rFSH versus rFSH (direct and indirect evidence)

Network estimates show that com ined uFSH and rFSH may result in little to no difference in clinical pregnancy versus rFSH (RR 1.21, 95% CI 0.83 to 1.77; low-certainty e idence; Figure 25).

uFSH & rFSH versus u SH (dire t and indirect evidence)

Network estimate show that combined uFSH & rFSH may result in little to no difference clinical pregnancy versus uFSH (RR 1.21, 95% CI 0.83 to 1.76, 1 study low-certainty evidence; Figure 25).

Remaining indirect comparisons

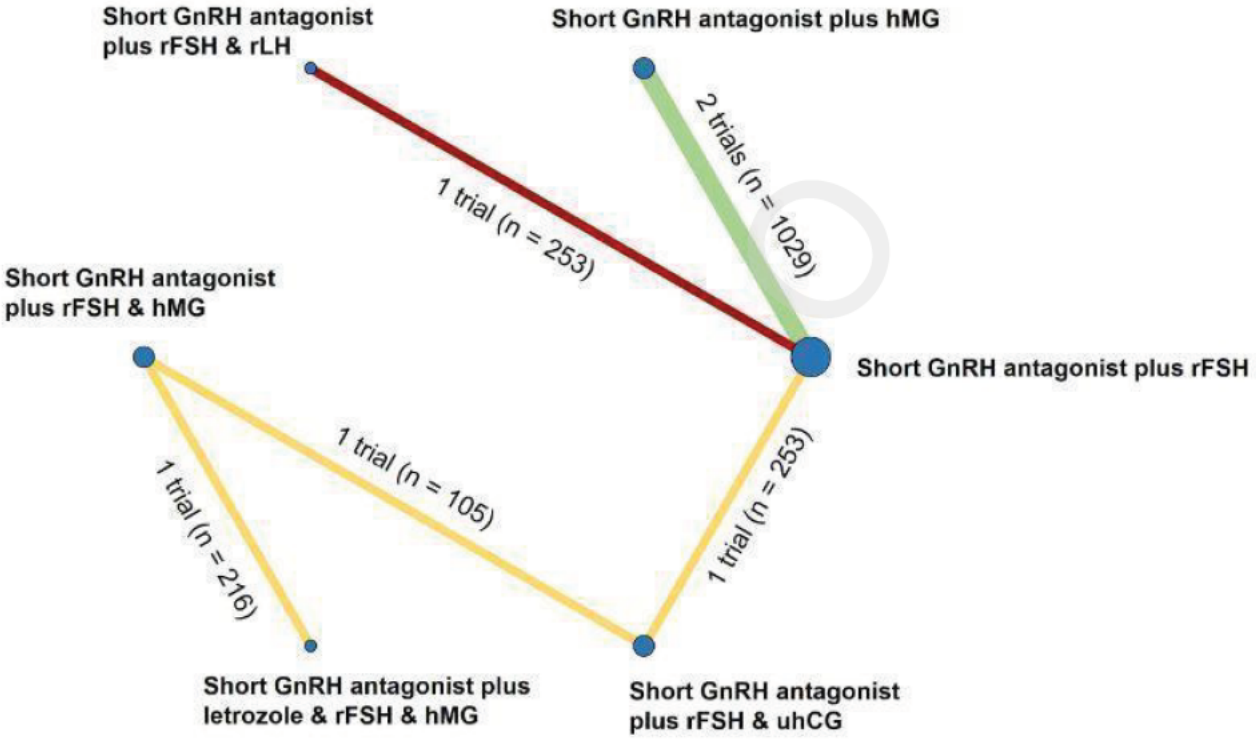
For the twenty remaining indirect comparisons, the network evidence is either uncertain or very uncertain (for effect estimates, see Figure 25).

Short GnRH antagonist protocols

Figure 26 presents the network diagram for clinical pregnancy in women with predicted normal response undergoing short GnRH antagonist protocols. The network was connected. There were five direct comparisons and then indirect comparisons.

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Figure 26. Network diagram of short GnRH antagonist protocols for the outcome of clinical pregnancy in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

hMG versus rFSH

Human menopausal gonadotrophin probably results in little to no difference in clinical p egnancy versus rFSH (RR 1.07, 95% 0.90 to 1.27, 2 studie , 1029 women, I^2 = 0%; moderate-certainty evidence; Analysis 7.3).

rFSH & rLH versus rF H

The evidence is very unce tain about this comparison (RR 0.91, 95% CI 0.57 to 1.48, 1 study, 253 women; very low-certainty evidence; Analysis 18.3).

rFSH & uhCG versus rFSH

Combined rFSH and uhCG may improve clinical pregnancy versus rFSH (RR 1.56, 95% CI 1.12 to 2.16, 1 study, 217 women; low-certainty evidence; Analysis 21.2).

rFSH & uhCG versus rFSH & hMG

Combined rFSH and uhCG may result in little to no difference in clinical pregnancy versus combined rFSH and hMG (RR 1.59, 95% CI 0.74 to 3.39, 1 study, 105 women; low-certainty evidence; Analysis 23.2).

Letrozole, rFSH & hMG versus rFSH & hMG

Combined letrozole, rFSH and hMG may reduce clinical pregnancy versus combined rFSH and hMG (RR 0.30, 95% CI 0.16 to 0.57, 1 study, 216 women; low-certainty evidence; Analysis 27.1).

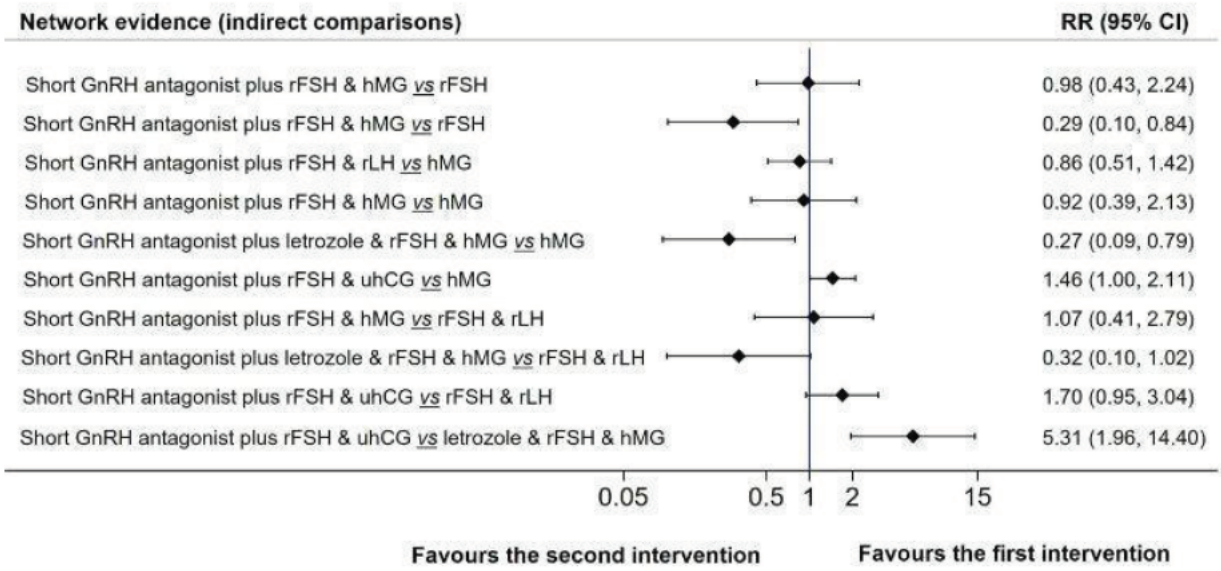
Network estimates (indirect evidence only)

rFSH & hMG versus rFSH

Network estimates show that rFSH & hMG may reduce clinical pregnancy versus rFSH (RR 0.29, 95% CI 0.10 to 0.84; low-certainty evidence; Figure 27).

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Figure 27. Forest plot comparing short GnRH antagonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of clinical pregnancy in women with predicted normal response.



Letrozole & rFSH & hMG versus hMG

Network estimates show that letrozole combined with rFSH and hMG may reduce clinical pregnancy vers hMG (RR 0.27, 95% CI 0.09 to 0.79; low-certainty evidence; Figure 27)

Remaining indirect comparisons

For the eight remaining i dir ct comparisons, the network evidence is either uncertain or very ncertain (for effect estimates, see Figure 27).

No pituitary supp essio

There was only one di ct comparison of protocols using ovarian stimulation without pitui ary suppression for the outcome of clinical pregnancy in women with predicted normal response (hMG versus uFSH).

hMG versus uFSH

The evidence is very uncertain about this comparison (RR 1.16, 95% CI 0.54 to 2.50, 1 study, 158 women; very low-certainty evidence; Analysis 30.1).

Other networks - GnRH agonist flare protocols; and progestogens for pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of clinical pregnancy in women with predicted normal response.

3.2. Women with predicted HIGH response

Pituitary suppression methods

There was only one comparison of pituitary suppression methods for the outcome of clinical pregnancy in women with predicted high response (short GnRH antagonist versus long GnRH agonist).

Short GnRH antagonist versus long GnRH agonist

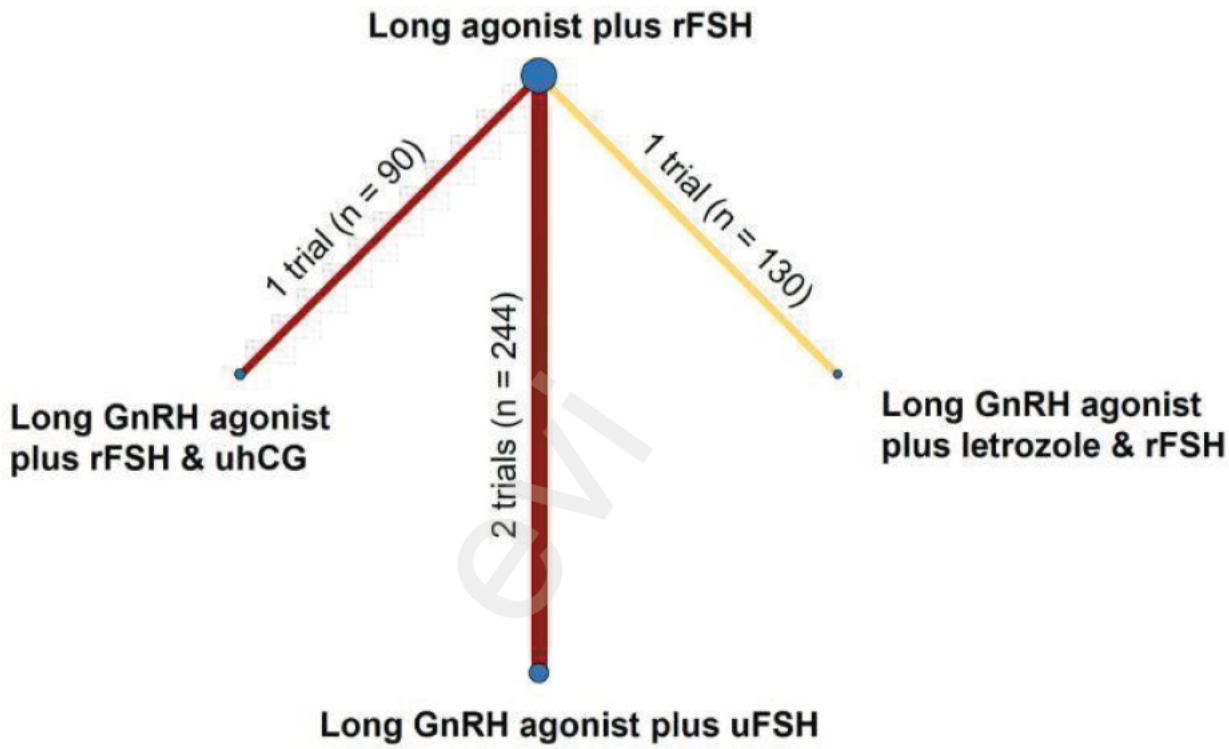
Short antagonist protocols may result in little to no difference in clinical pregnancy versus long agonist protocols (RR 0.85, 95% CI 0.68 to 1.07, 1 study, 220 women; low-certainty evidence; Analysis 1.3).

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Long GnRH agonist protocols

Figure 28 shows the network diagram for clinical pregnancy in women with predicted high response undergoing long GnRH agonist protocols. The network was connected. There were three direct comparisons and three indirect comparisons.

Figure 28. Network diagram of long GnRH agonist protocols for the outcome of clinical pregnancy in women with predicted high response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

uFSH versus rFSH

The evidence is very uncertain about this comparison (RR 1.03, 95% CI 0.79 to 1.35, 2 studies 244 women, I^2 = 0%; very low-certainty evidence; Analysis 6.3).

Letrozole & rFSH versus rFSH

Combined letrozole and rFSH may result in little to no difference in clinical pregnancy versus rFSH (RR 0.74, 95% CI 0.51 to 1.08, 1 study, 130 women; low-certainty evidence; Analysis 9.3).

rFSH & uhCG versus rFSH

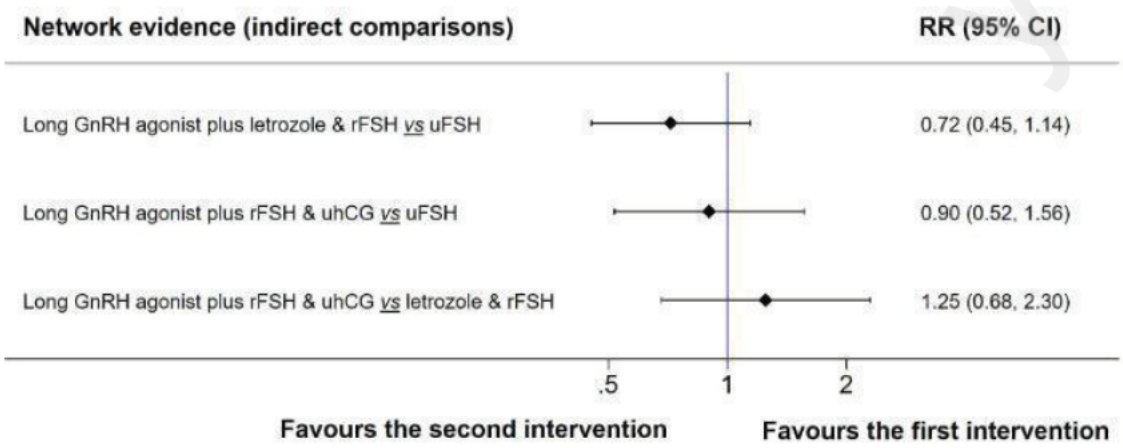
The evidence is very uncertain about this comparison (RR 0.93, 95% CI 0.57 to 1.50, 1 study, 90 women; very low-certainty evidence; Analysis 14.3).

Network estimates (indirect evidence)

For the three indirect comparisons, the network evidence is very uncertain (for effect estimates, see Figure 29).

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Figure 29. Forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of clinical pregnancy in women with predicted high response.



Other networks - short GnRH antagonist protoc ls; GnRH agonist flare protocols; progestogens f r pi uitary uppression; and ovarian stimulation without pitu tary suppression

The primary analysis did not include ny studies comparing interventions within these networks for th outcome of clinical pregnancy in women with predicted high response.

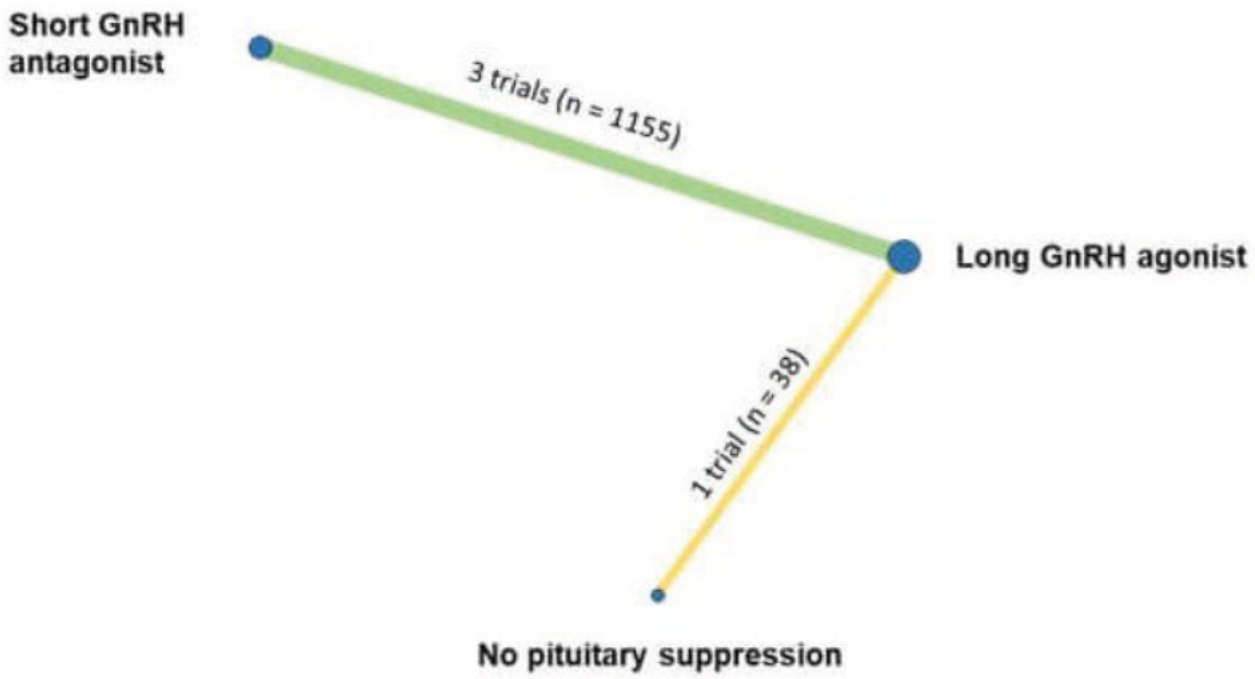
3.3. Women with predicted LOW response

Pituitary suppression methods

Figure 30 shows the primary network diagram of pituitary suppression methods for the outcome of clinical pregnancy in women with predicted low response. The network was connected. There were two direct comparisons and one indirect comparison.

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Figure 30. Network diagram of pituitary suppression methods for the outcome of clinical pregnancy in women with predicted low response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence and amber for low-certainty evidence.



Direct comparisons

Short GnRH antagonist versus long GnRH agonist

Short antagonist protocols probably result in little to no difference in clinical pregnancy versus long agonist protocols (RR 0.93, 95% CI 0.71 to 1.24, 3 studies, 1155 women, $I^2 = 0\%$; moderate-certainty evidence; Analysis 3.3).

No pituitary suppression versus long GnRH agonist

Protocols without pituitary suppression may result in little to no difference in clinical pregnancy versus long GnRH agonist protocols (RR 0.96, 95% CI 0.29 to 3.23, 1 study, 38 women; low-certainty evidence; Analysis 3.2).

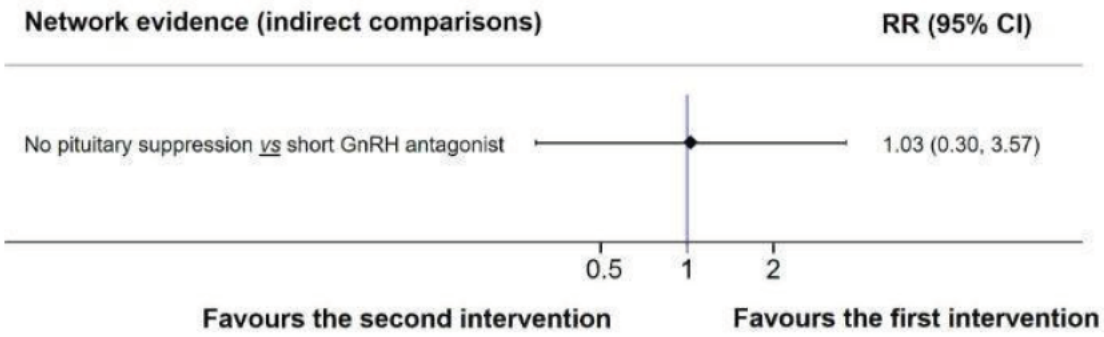
Network estimates (indirect evidence only)

No pituitary suppression versus short GnRH antagonist

Network estimates show that ovarian stimulation without pituitary suppression may result in little to no difference in clinical pregnancy versus short GnRH antagonist protocols (RR 1.03, 95% CI 0.30 to 3.57; low-certainty evidence; Figure 31).

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Figure 31. Forest plot comparing pituitary suppression methods with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of clinical pregnancy in women with predicted low response.



Long GnRH agonist protocols

There was only one comparison for clinical pregnancy in women with predicted low response undergoing long GnRH agonist protocols (rFSH & rLH versus rLH).

rFSH & rLH versus rFSH

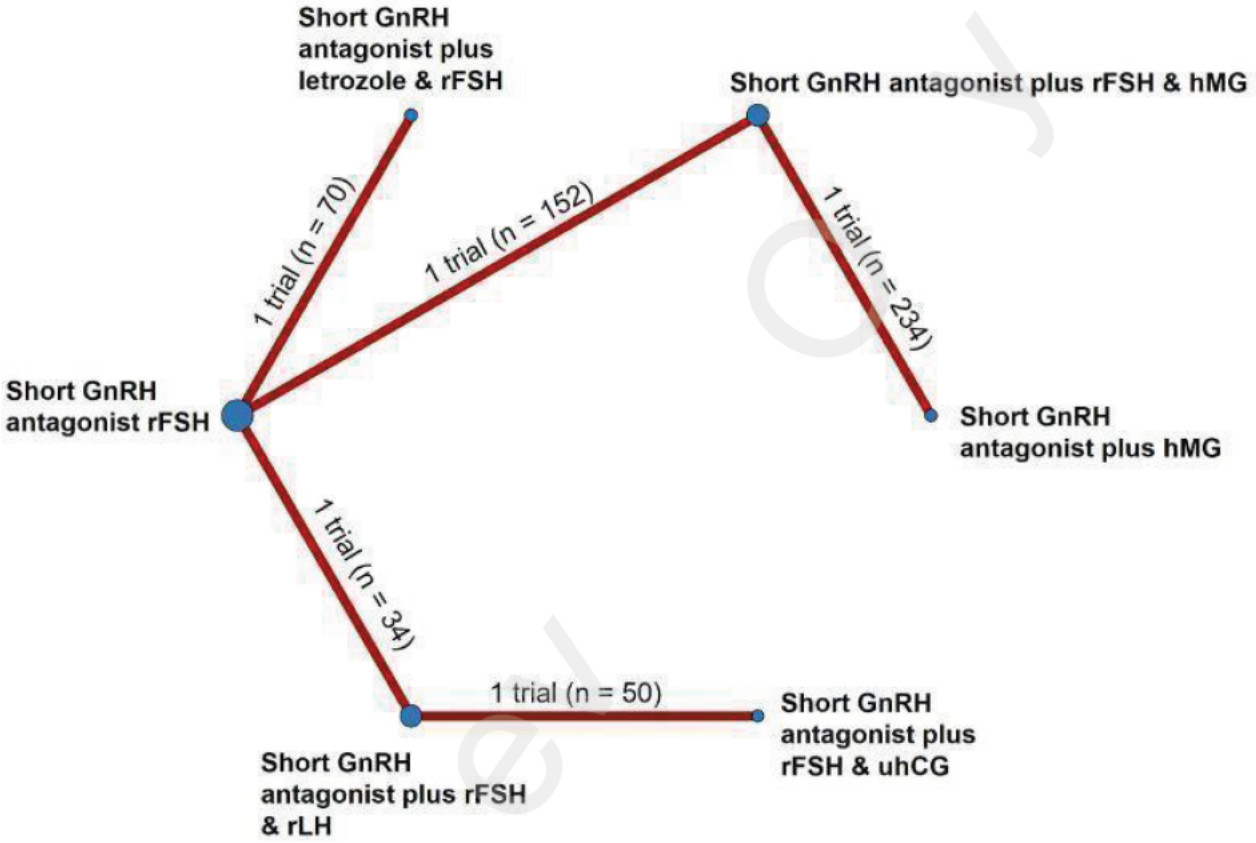
Combined rFSH and rLH may result in little to no difference in clinical pregnancy versus rFSH (RR 0.87, 95% CI 0.66 to 1.14, 2 studies, 1183 women, I^2 = 0%; low-certainty evidence; Analysis 10.3).

Short GnRH antagonist protocols

Figure 32 presents the network diagram for clinical pregnancy in women with predicted low response undergoing short GnRH antagonist protocols. The network was connected. There were five direct comparisons and ten indirect comparisons. The evidence is very uncertain for all direct (Analysis 18.3, Analysis 19.2, Analysis 20.3, Analysis 22.2 and Analysis 26.1) and indirect (Figure 33) comparisons.

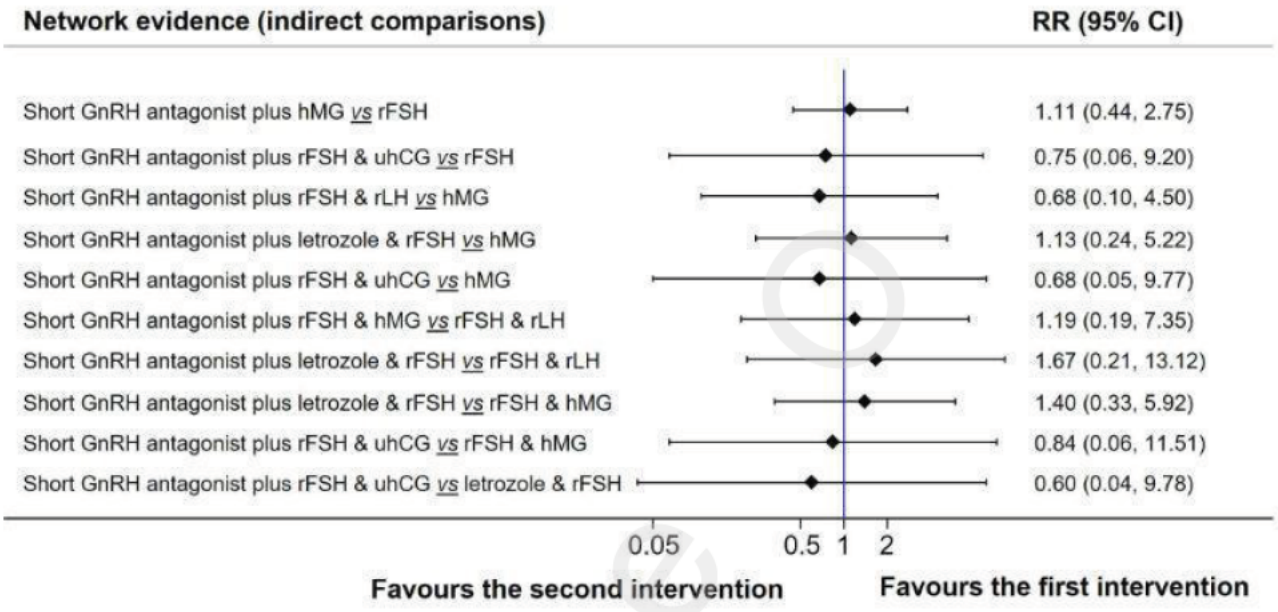
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Figure 32. Network diagram of short GnRH antagonist protocols for the outcome of clinical pregnancy in women with predicted low response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is red for very low-certainty evidence.



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Figure 33. Forest plot comparing short GnRH antagonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (dindirect comparisons only) for the outcome of clinical pregnancy in women with predicted low response.



Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of clinical pregnancy in women with predicted low response.

4. Ongoing pregnancy

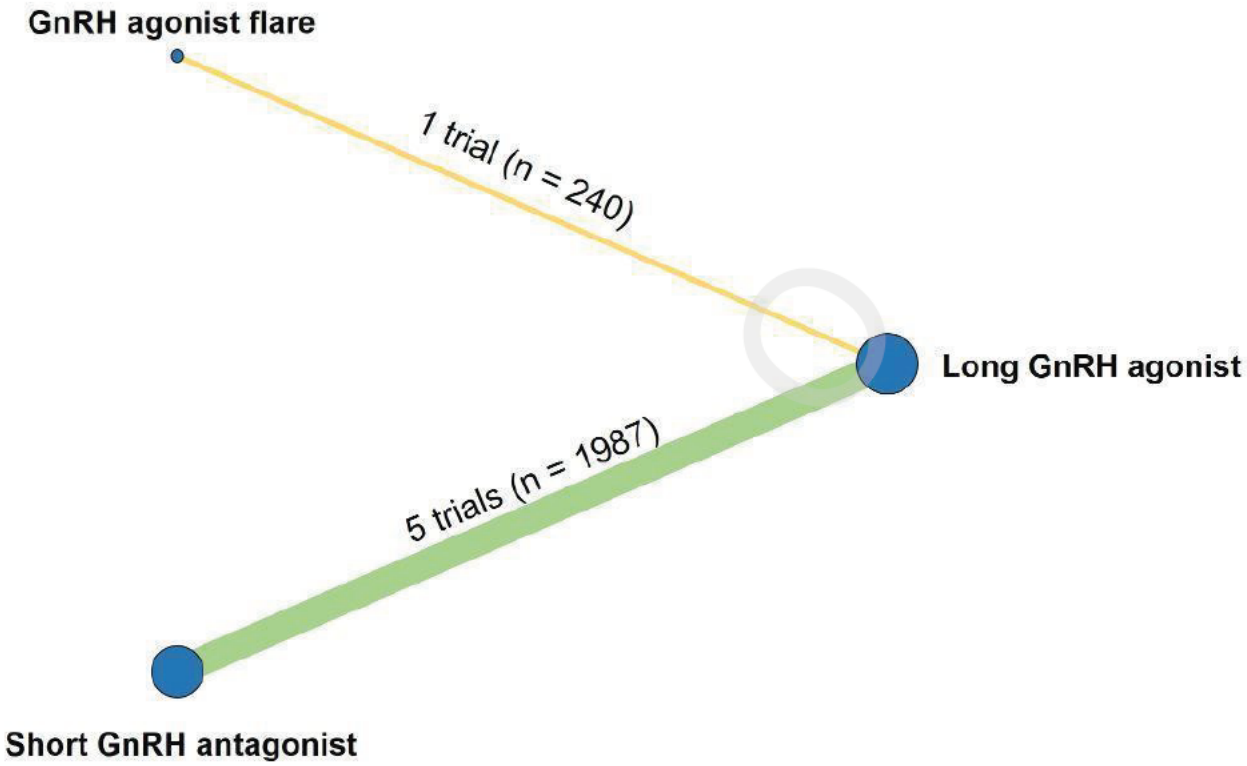
4.1. Women with predicted NORMAL response

Pituitary suppression methods

Figure 34 shows the primary network diagram of pituitary suppression methods for the outcome of ongoing pregnancy in women with predicted normal response. The network was connected. There were two direct comparisons and one indirect comparison.

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Figure 34. Network diagram of pituitary suppression methods for the outcome of ongoing pregnancy in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence and amber for low-certainty evidence.



Direct comparisons

Short GnRH antagonist versus long GnRH a onist

Short antagonist protocols probably esult in ittle to no difference in ongoing pregnancy versus long ago st p otocols (RR 0.94, 95% CI 0.82 to 1.07, 5 studies, 1987 women, I^2 = %; moderate-certainty evidence; Analysis 1.4).

GnRH agonist flare versus long GnRH agonist

GnRH agonist flare protocols may result in little to no difference in ongoing pregnancy versus long GnRH agonist protocols (RR 1.23, 95% CI 0.92 to 1.63, 1 study, 240 women; low-certainty evidence; Analysis 2.3).

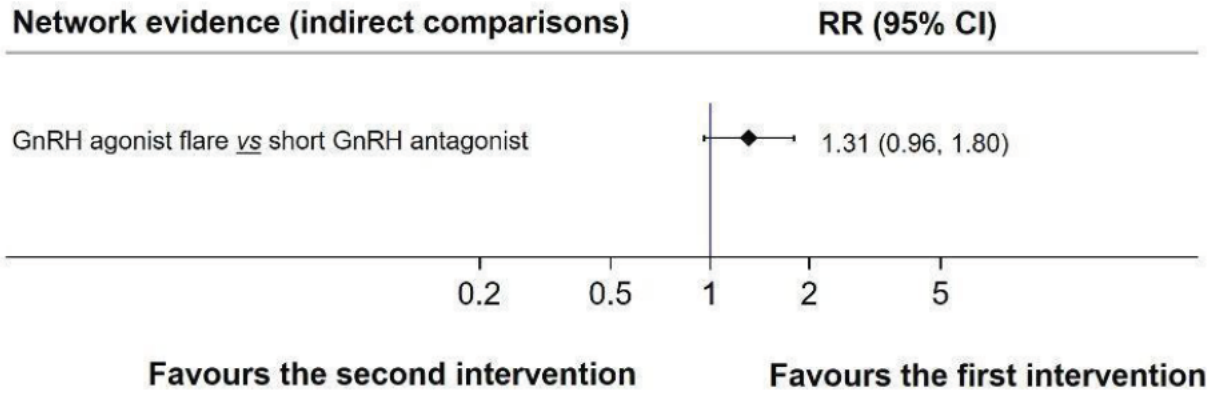
Network estimates (indirect evidence only)

GnRH agonist flare versus short GnRH antagonist

GnRH agonist flare protocols may result in little to no difference in ongoing pregnancy versus short GnRH antagonist protocols (RR 1.31, 95% CI 0.96 to 1.80; low-certainty evidence; Figure 35).

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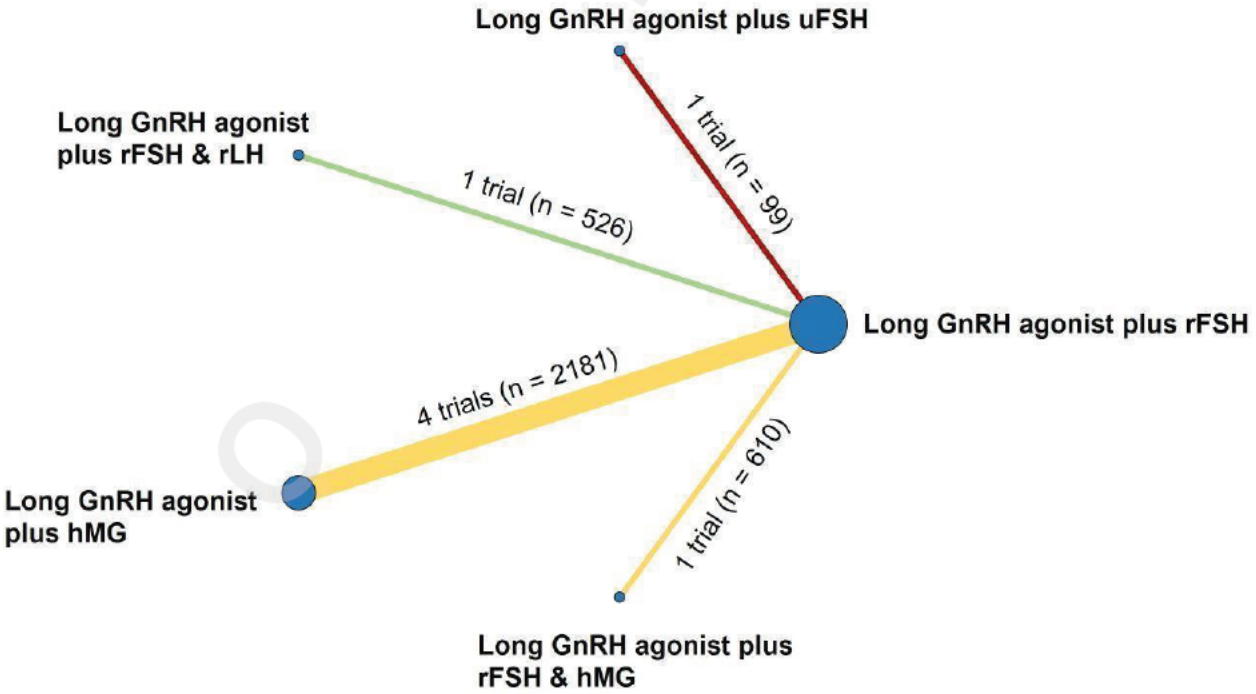
Figure 35. Forest plot comparing pituitary suppression methods with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of ongoing pregnancy in women with predicted normal response.



Long GnRH agonist protocols

Figure 36 shows the network diagram for ongoing pregnancy in women with predicted normal response undergoing long GnRH agonist protocols. The network was connected. There were four direct comparisons an six indirect comparisons.

Figure 36. Network diagram of long GnRH agonist protocols for the outcome of ongoing pregnancy in women with predicted normal response. The nodes represent an intervention a d heir size is proportional to the number of trials comparing this intervention to any other in the netwo k Th lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The number on th lines represent the number of trials and in brackets the number of participants evaluated within each ompari on. he colour of the line is green for moderate-certainty evidence; amber for low-certainty evidence; and red fo very low-certainty evidence.



Direct comparisons

uFSH versus rFSH

The evidence is very uncertain about this comparison (RR 0.54, 95% CI 0.23 to 1.26, 1 study, 99 women; very low-certainty evidence; Analysis 6.4).

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hMG versus rFSH

Human menopausal gonadotrophin may result in little to no difference in ongoing pregnancy versus rFSH (RR 1.13, 95% CI 0.97 to 1.32, 4 studies, 2181 women, I^2 = 0%; low-certainty evidence; Analysis 7.4).

rFSH & rLH versus rFSH

Combined rFSH and rLH probably results in little to no difference in ongoing pregnancy versus rFSH (RR 0.95, 95% CI 0.72 to 1.24, 1 study, 526 women; moderate-certainty evidence; Analysis 10.4).

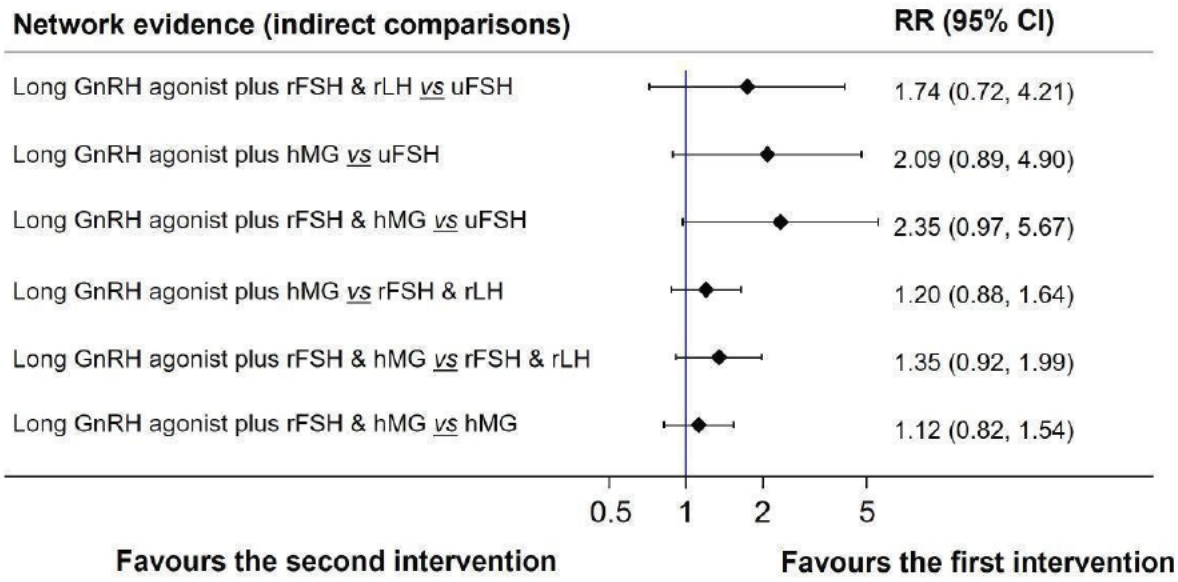
rFSH & hMG versus rFSH

Combined rFSH and hMG may result in little to no difference in ongoing pregnancy versus rFSH (RR 1.28, 95% CI 0.97 to 1.67, 1 study, 610 women; low-certainty evidence; Analysis 15.3).

Network estimates (indirect evidence only)

For the seventeen remaining comparisons, the network evidence is either uncertain or very uncertain (for effect estimates, see Figure 37).

Figure 37. Forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of ongoing pregnancy in women with predicted normal response.

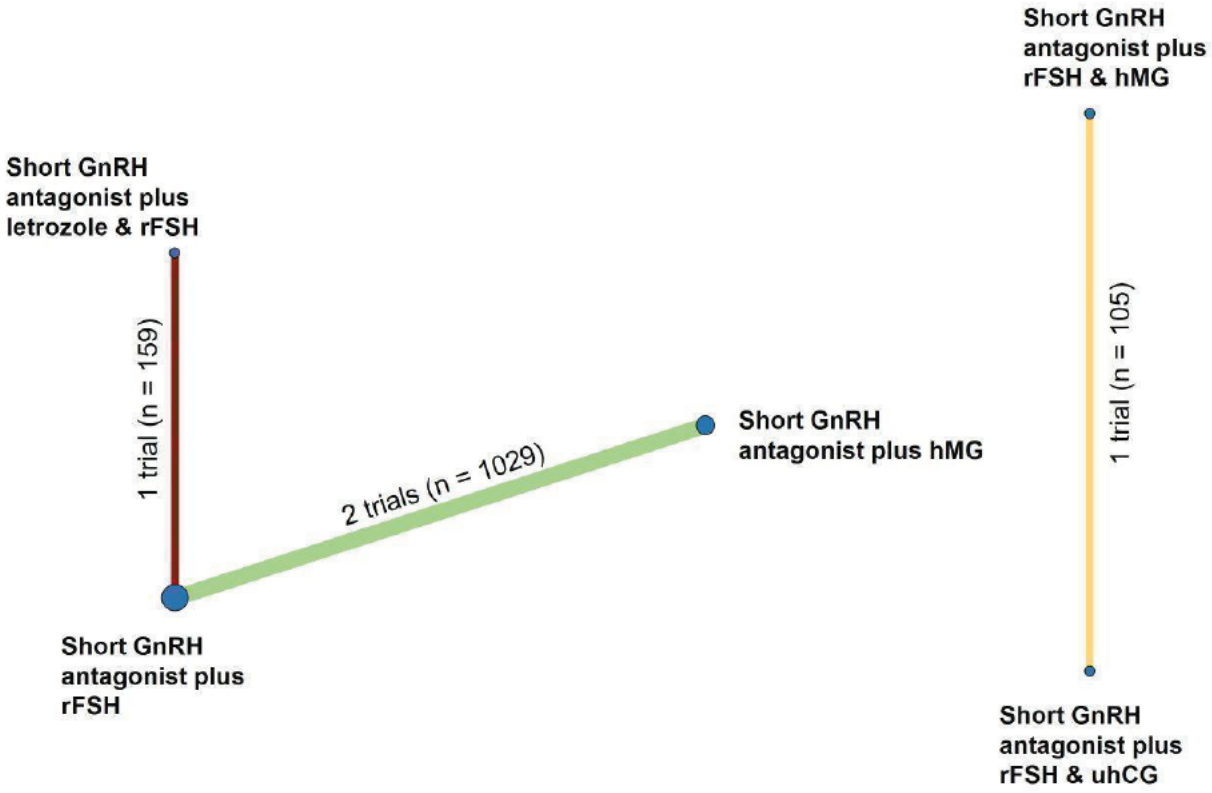


Short GnRH antagonist protocols

Figure 38 shows the network diagram for o going pregnancy in women with predicted normal resp nse undergoing short GnRH antagonist protocols. The network was disconnected. There were three direct comparisons and one indirect comparison.

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Figure 38. Network diagram of short GnRH antagonist protocols for the outcome of ongoing pregnancy in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

hMG versus rFSH

Human menopausal gonadotrophin probably results in little to no difference in ongoing pregnancy vers rFSH (RR 1.08, 95% CI 0.89 to 1.30, 2 studies, 1029 women, I^2 = 0%; moderate-certainty evidence; Analysis 17.4).

rFSH & uhCG versus rFSH & hMG

Combined rFSH and uhCG may res lt in little to no difference in ongoing pregnancy versus combine rFSH and hMG (RR 1.38, 95% CI 0.59 to 3.21, 1 study, 105 women; low-certainty evidence; Analysis 23.3).

Letrozole & rFSH versus rF H

The evidence is very uncertain about this comparison (RR 0.80, 95% CI 0.49 to 1.29, 1 study, 159 women; very low-certainty evidence; Analysis 26.2).

Network estimates (indirect evidence only)

For the remaining indirect comparison, the network evidence is very uncertain.

No pituitary suppression

The quantitative analysis included only one direct comparison of protocols using ovarian stimulation without pituitary suppression for the outcome of ongoing pregnancy in women with predicted normal response (hMG versus uFSH).

hMG versus uFSH

The evidence is very uncertain about this comparison (RR 0.96, 95% CI 0.41 to 2.26, 1 study, 158 women; very low-certainty evidence; Analysis 30.2).

Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of ongoing pregnancy in women with predicted normal response.

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4.2. Women with predicted HIGH response

Pituitary suppression methods

There was only one comparison of pituitary suppression methods for the outcome of ongoing pregnancy in women with predicted high response (short GnRH antagonist versus long GnRH agonist protocols).

Short GnRH antagonist versus long GnRH agonist

Short antagonist protocols probably result in little to no difference in ongoing pregnancy versus long agonist protocols (RR 0.97, 95% CI 0.77 to 1.15, 3 studies, 576 women, I^2 = 0%; moderate-certainty evidence; Analysis 1.4).

Long GnRH agonist protocols

There was only one comparison for ongoing pregnancy in women with predicted high response undergoing long GnRH agonist protocols (uFSH versus rFSH).

uFSH versus rFSH

The evidence is very uncertain about this comparison (RR 1.08, 95% CI 0.78 to 1.48, 2 studies, 244 women, I^2 = 0%; very low-certainty evidence; Analysis 6.4).

Short GnRH antagonist protocols

There was only one comparison for ongoing pregnancy in women with predicted high response undergoing short GnRH antagonist protocols (hMG versus rFSH).

hMG versus rFSH

Human menopausal gonadotrophin may result in little to no difference in ongoing pregnancy versus rFSH (RR 1.15, 95% CI 0.92 to 1.45, 1 study, 619 women; low-certainty evidence; Analysis 17.4).

Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did n t includ any studies comparing interventions within thes networks for the outcome of ongoing pregnancy in women with predicted high response.

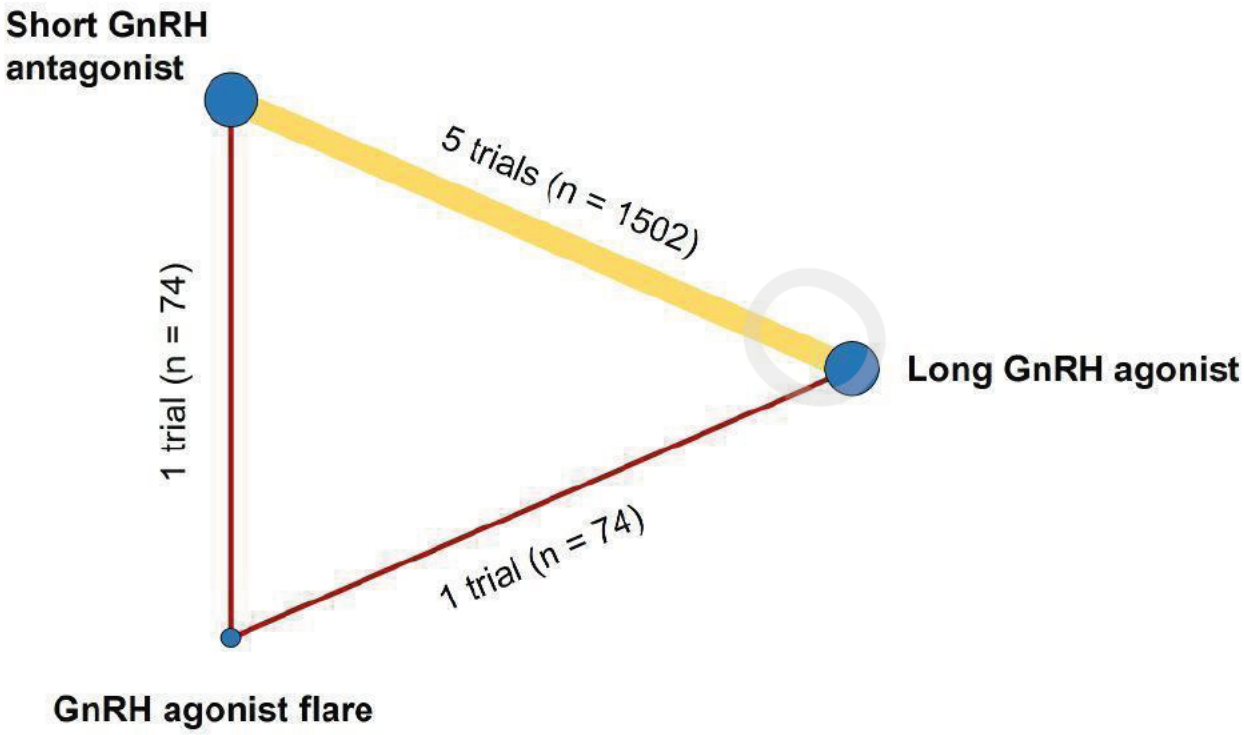
4.3. Women with pr dicted LOW response

Pituitary uppression methods

Figure 39 shows the primary network diagram of pituitary suppression methods for the outcome of ongoing pregnancy in women with predicted low response. The network was connected. There w re three comparisons for which it was possible to obtain net ork es imates from direct and indirect evidence.

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Figure 39. Network diagram of pituitary suppression methods for the outcome of ongoing pregnancy in women with predicted low response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence; and red for very low-certainty evidence.

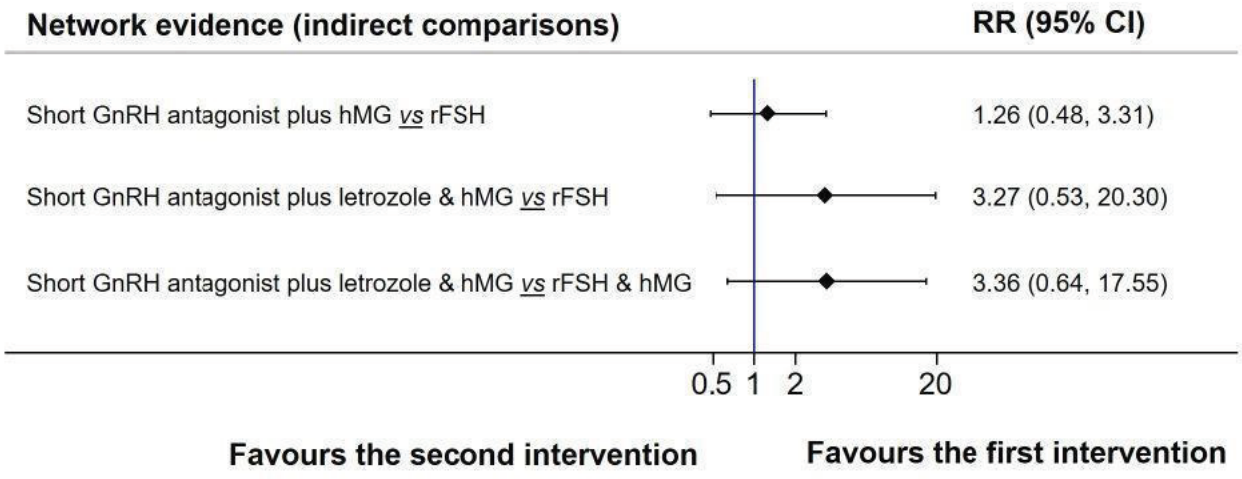


Network evidence (direct and indirect evidence)

Short GnRH antagonist versus long GnRH agonist

Short GnRH antagonist protocols may result in little to no difference in ongoing pregnancy versus long GnRh agonist protocols (RR 0.88, 95% CI 0.67 to 1.16; low-certainty evidence; Figure 40).

Figure 40. Forest plot comparing short GnRH antagonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network me analysis (indirect comparisons only) for the outcome of ongoing pregnancy in women with predicted low respons

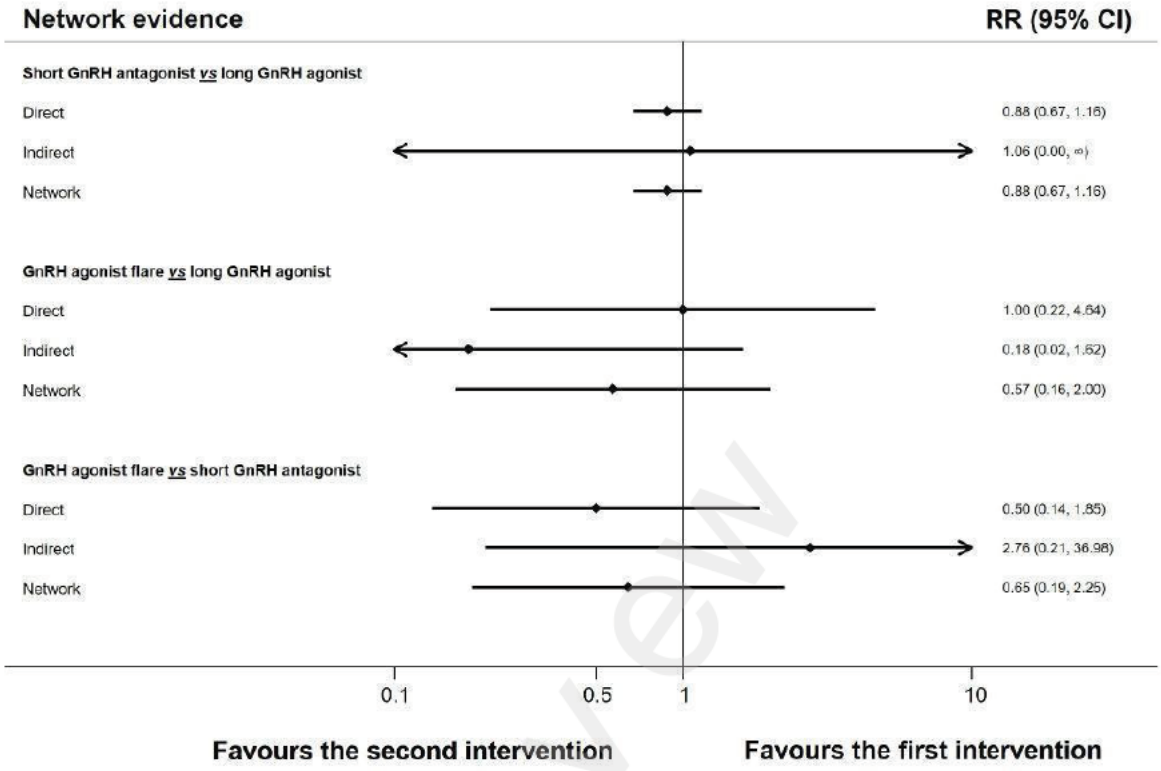


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Remaining comparisons

For the two remaining comparisons, the network evidence is very uncertain (for effect estimates, see Figure 41).

Figure 41. Forest plot comparing pituitary suppression methods with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (direct, indirect and network estimates) for the outcome of ongoing pregnancy in women with predicted low response.



Long GnRH agonist protocols

There was only one direct comparison for ongoing pregnancy in women with predicted low response unde g ing lo g GnRH agonist protocols (rFSH & rLH versus rFSH)

rFSH & rLH versus rFSH

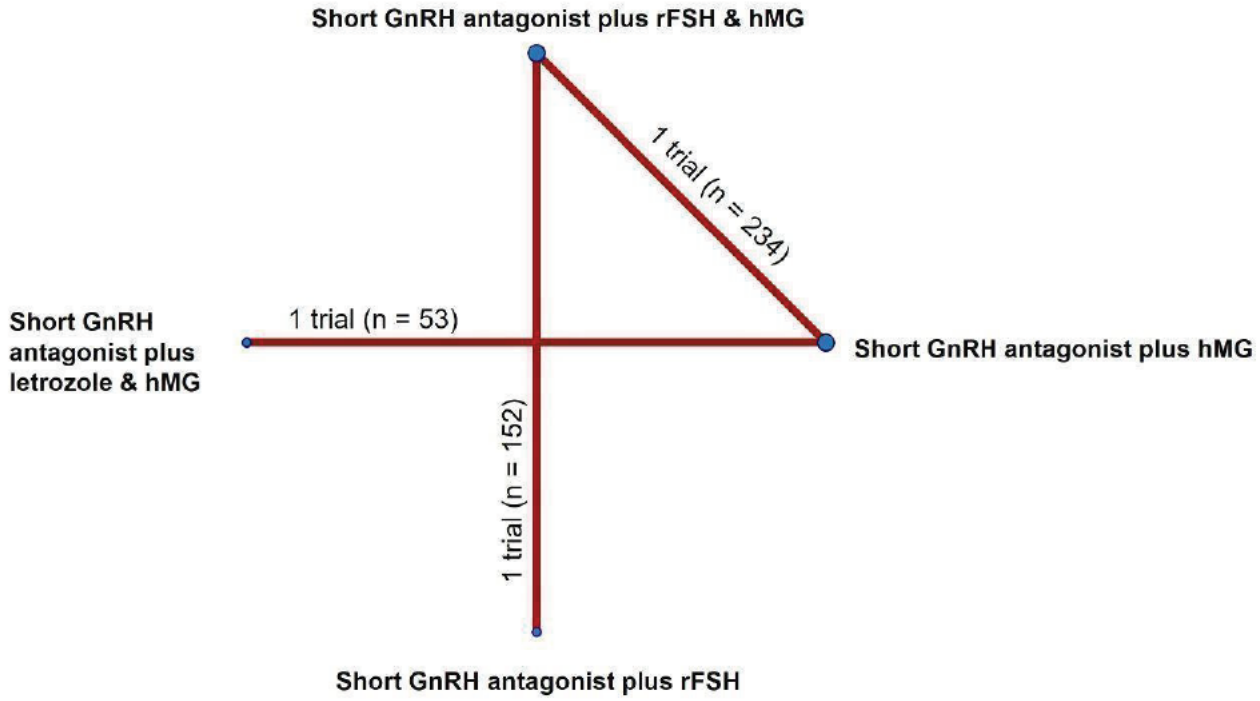
Combined rFSH and rLH may result in little to no difference in ongoing pregnancy versus rFSH RR 1.02, 95% CI 0.78 to 1.35, 3 studies, 1313 women, I^2 = 0%; low-certainty evidence; Analysis 10.4).

Short GnRH antagonist protocols

Figure 42 shows the network diagram for ongoing pregnancy in women with predicted low response undergoing short GnRH antagonist protocols. The network was connected. There were three direct comparisons and three indirect comparisons. The evidence is very uncertain for all direct (Analysis 19.3, Analysis 20.4 and Analysis 25.2) and network (Figure 40) estimates.

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Figure 42. Network diagram of short GnRH antagonist protocols for the outcome of ongoing pregnancy in women with predicted low response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is red for very low-certainty evidence.



Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of ongoing pregnancy in women with predicted low response.

5. Multiple pregnancy

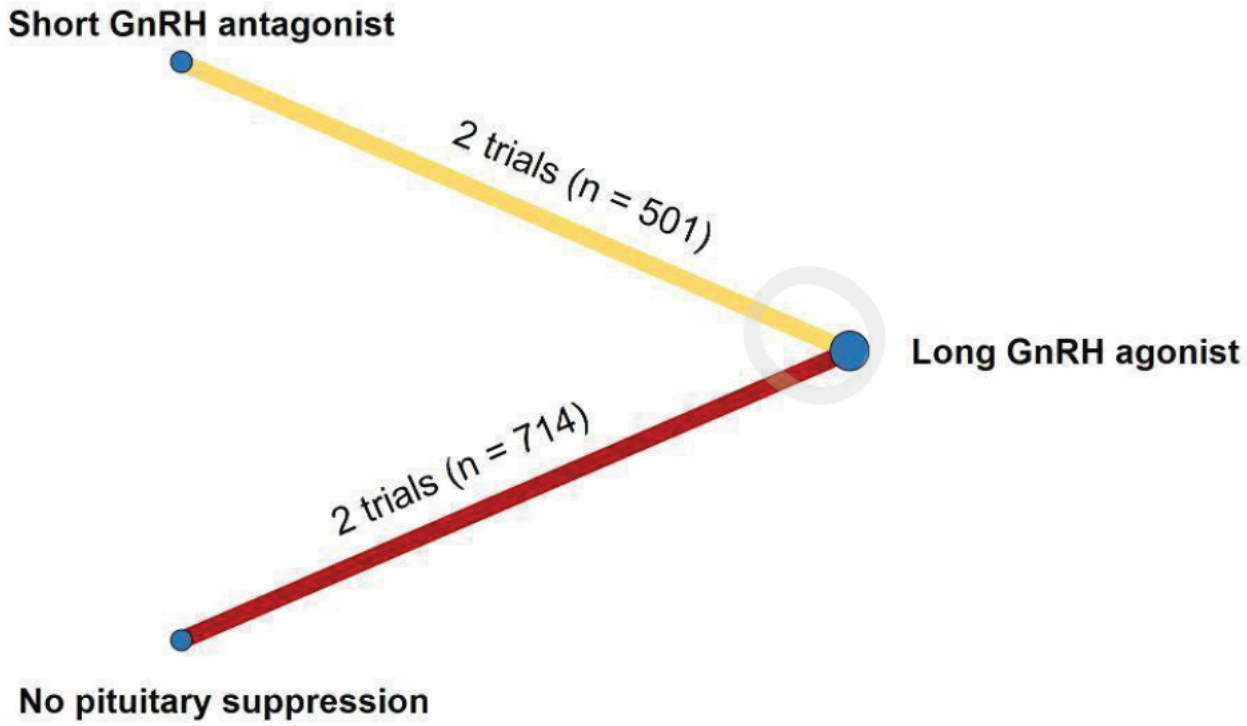
5.1. Women with predicted NORMAL response

Pituitary suppression methods

Figure 43 shows the primary network diagram of pituitary suppression methods for the outcome of multiple pregnancy in women with predicted normal response. The network was connected. There were two direct comparisons and one indirect comparison.

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Figure 43. Network diagram of pituitary suppression methods for the outcome of multiple pregnancy in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparisons

Short GnRH antagonist versus long GnRH agonist

Short GnRH antagonist protocols may re ult little o no difference in multiple pregnancy versus long GnRH agon t protocols (RR 0.92, 95% CI 0.51 to 1.65, 2 studies, 501 w men ^{2} = 0%; low-certainty evidence; Analysis 1.5).

No pituitary suppression versus long GnRH agonist

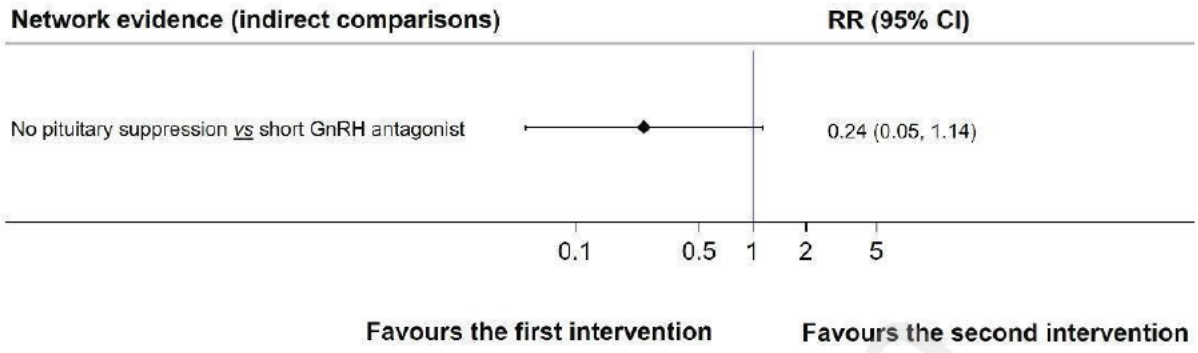
The evidence is very uncertain about this comparison (RR 0.27, 95% CI 0.07 to 1.04, 2 studies, 714 women, I^2 = 72%; very low-certainty evidence; Analysis 3.3).

Network estimates (indirect evidence only)

The network evidence for the remaining indirect comparison is very uncertain (for effect estimates, see Figure 44).

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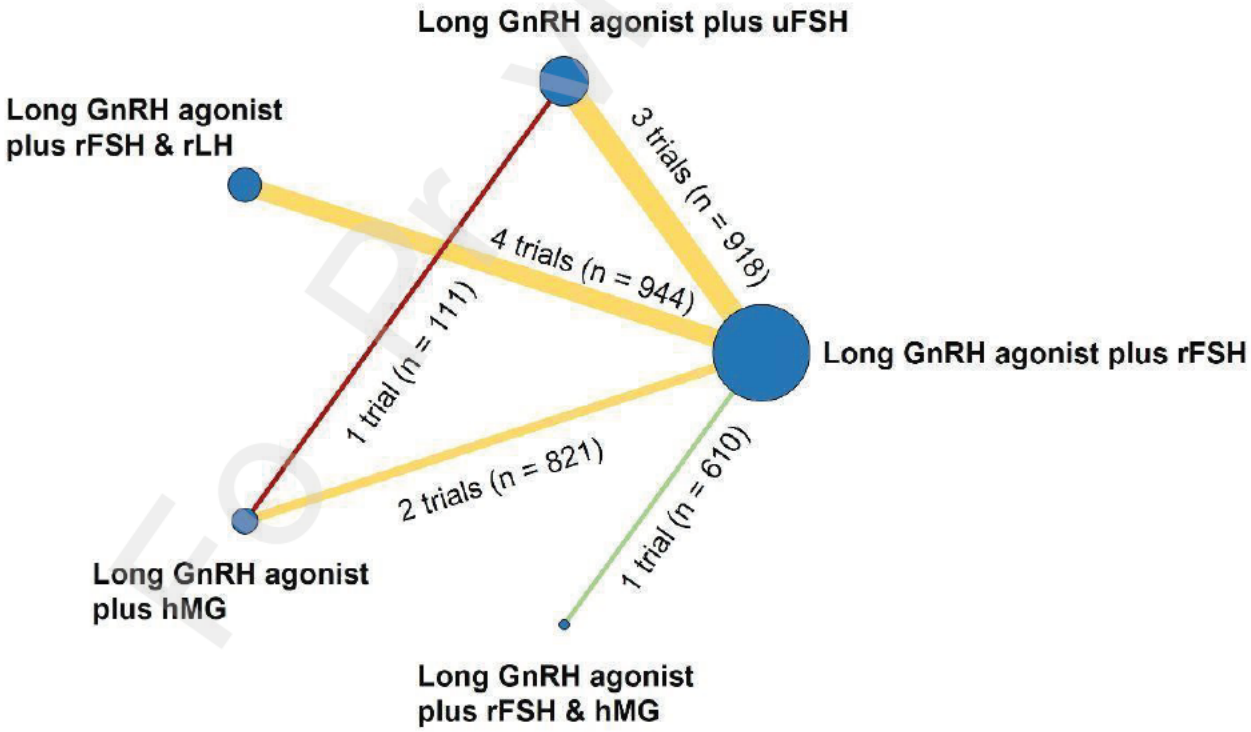
Figure 44. Forest plot comparing pituitary suppression methods with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of multiple pregnancy in women with predicted normal response.



Long GnRH agonist protocols

Figure 45 shows the network diagram for multiple pregnancy in women with predicted normal response undergoing long GnRH agonist protocols. There were two comparisons for which only direct evidence was available; three comparisons for which both direct and indirect evidence were available; and five comparisons for which only indirect evidence was available.

Figure 45. Network diagram of long GnRH agonist protocols for the outcome of multiple pregnancy in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

rFSH & rLH versus rFSH

Combined rFSH and rLH may result in little to no difference in multiple pregnancy versus rFSH (RR 1.13, 95% CI 0.63 to 2.02, 4

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studies, 944 women, I^2 = 17%; low-certainty evidence; Analysis 10.5).

rFSH & hMG versus rFSH

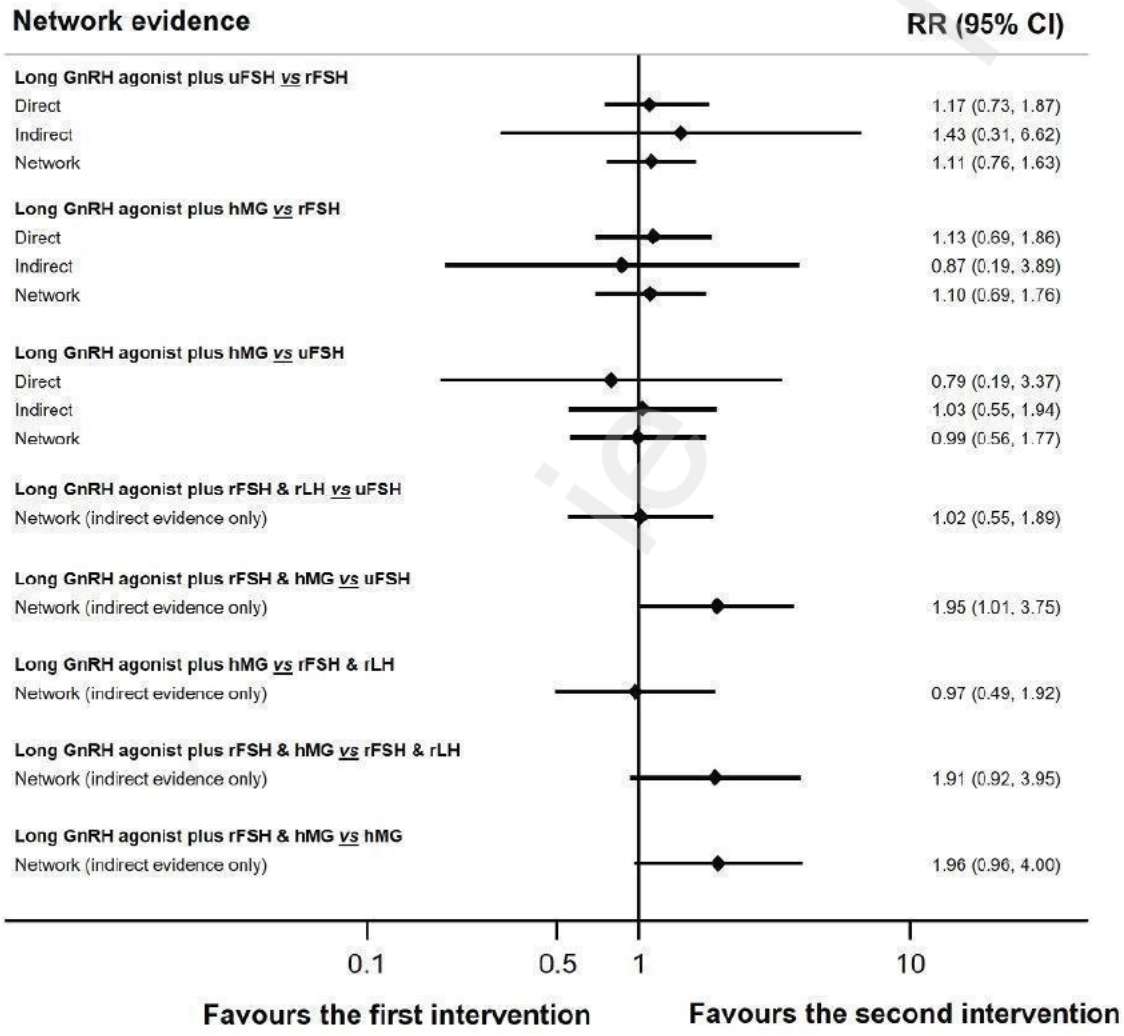
Combined rFSH and hMG probably increases multiple pregnancy versus rFSH (RR 2.17, 95% 1.27 to 3.70, 1 study, 610 women; moderate-certainty evidence; Analysis 15.4).

Network estimates (direct and indirect comparisons)

uFSH versus rFSH

Urinary FSH may result in little no difference in multiple pregnancy versus rFSH (RR 1.11, 95% CI 0.76 to 1.63; low-certainty evidence; Figure 46).

Figure 46. Forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (direct, indirect and network estimates; where no RCTs were conducted for a specific comparison, only the indirect [network] estimate is presented) for the outcome of multiple pregnancy in women with predicted normal response.



hMG versus rFSH

Human menopausal gonadotrophin may result in little to no difference in multiple pregnancy versus rFSH (RR 1.10, 95% CI 0.69 to 1.76; low-certainty evidence; Figure 46).

hMG versus uFSH

The evidence is very uncertain about this comparison (RR 0.99, 95% CI 0.56 to 1.77; very low-certainty evidence; Figure 46).

Remaining indirect comparisons

For the remaining five indirect comparisons, the network evidence suggests that each intervention results in little to no difference in multiple pregnancy versus its comparator (low-certainty evidence; for effect estimates, see Figure 46).

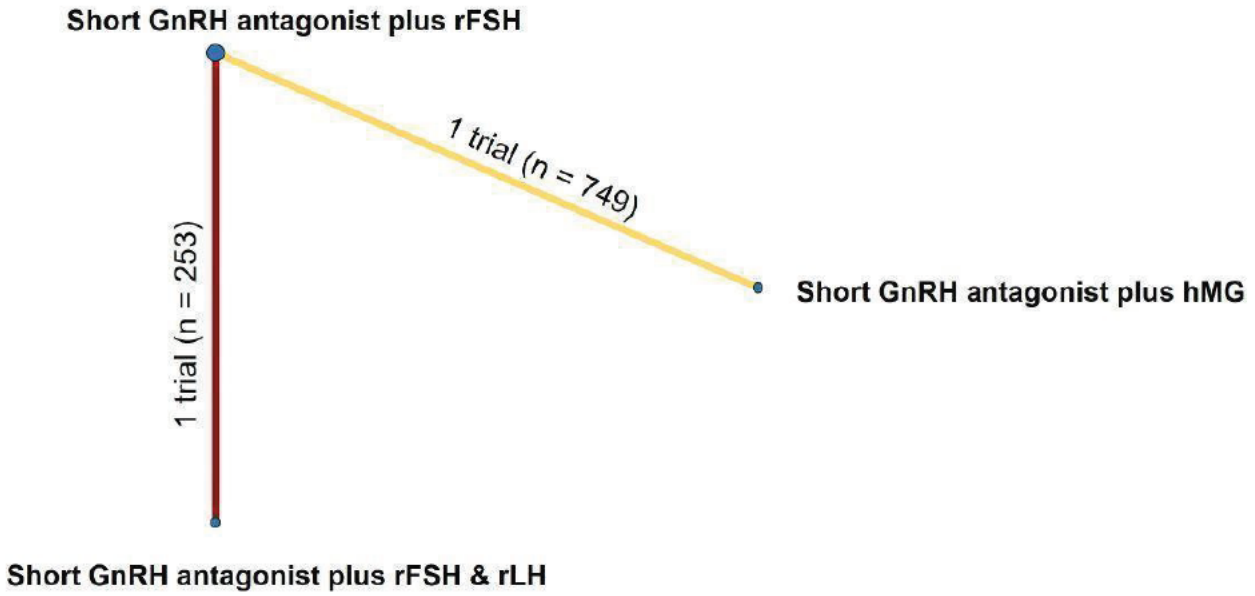
Short GnRH antagonist protocols

Figure 47 shows the network diagram for multiple pregnancy in women with predicted normal response undergoing short GnRH

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antagonist protocols. The network was connected. There were two direct comparisons and one indirect comparison.

Figure 47. Network diagram of short GnRH antagonist protocols for the outcome of multiple pregnancy in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparisons

hMG versus rFSH

Human menopausal gonadotrophin may result in little to no difference in multiple pregnancy versus rFSH (RR 9.02, 95% CI 0.49 to 167.02, 1 study, 749 women; low-certainty evidence; Analysis 17.5).

rFSH & rLH versus rFSH

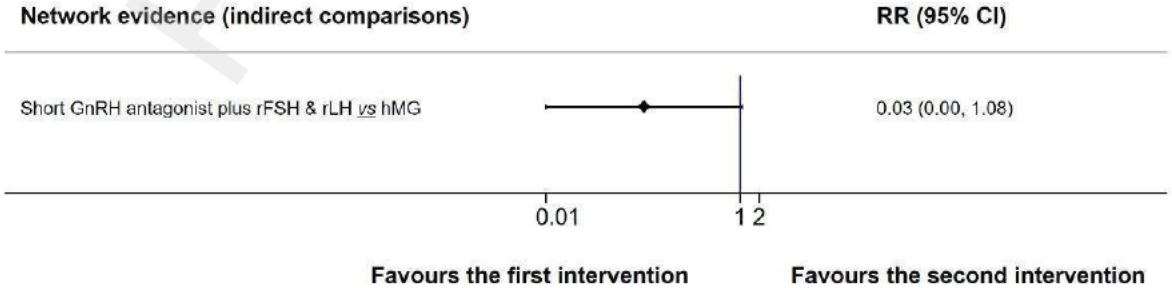
The evidence is very uncertain about this comparison (RR 0.26, 95% CI 0.03 to 2.26, 1 study, 253 women; very low-certainty evidence; Analysis 18.4).

Network estimates (indirect evidence only)

rFSH & rLH versus hMG

The evidence is very uncertain about this comparison (RR 0.03, 95% CI 0 to 1.08; very low-certainty evidence; Figure 48).

Figure 48. Forest plot comparing short GnRH antagonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect evidence only) for the outcome of multiple pregnancy in women with predicted normal response.



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Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of multiple pregnancy in women with predicted normal response.

5.2. Women with predicted HIGH response

Pituitary suppression methods

There was only one comparison between pituitary suppression methods for the outcome of multiple pregnancy in women with predicted high response (short GnRH antagonist versus long GnRH agonist).

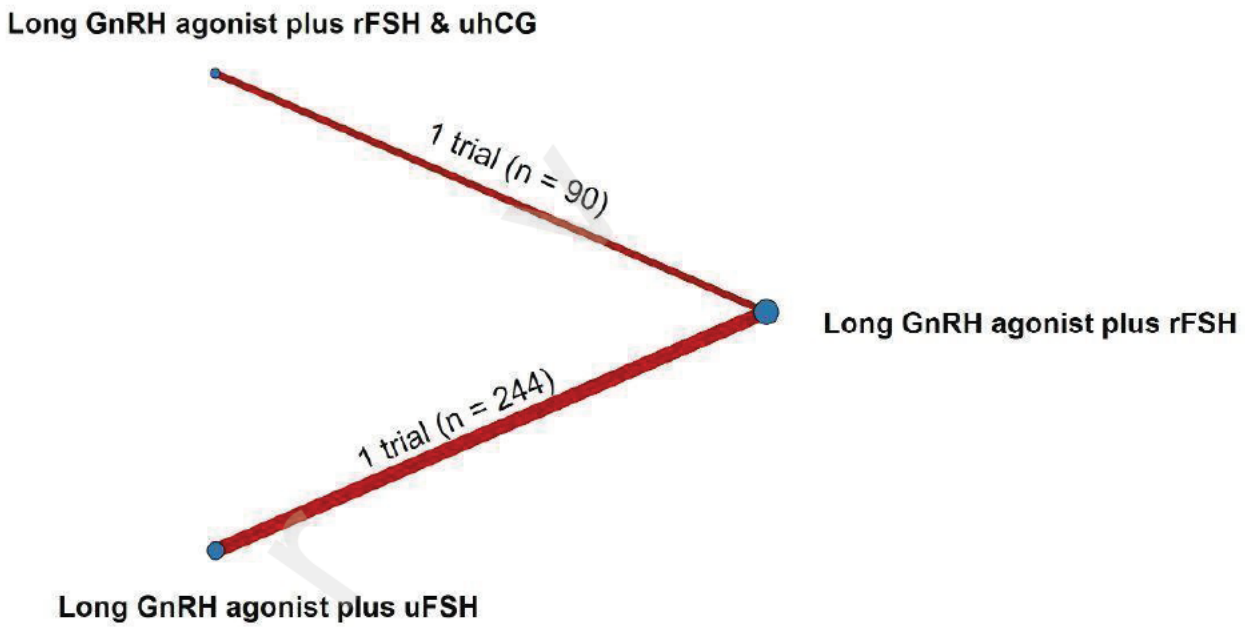
Short GnRH antagonist versus long GnRH agonist

Short antagonist protocols may result in little to no difference in multiple pregnancy versus long agonist protocols (RR 0.90, 95% CI 0.38 to 2.15, 1 study, 300 women; low-certainty evidence; Analysis 1.5).

Long GnRH agonist protocols

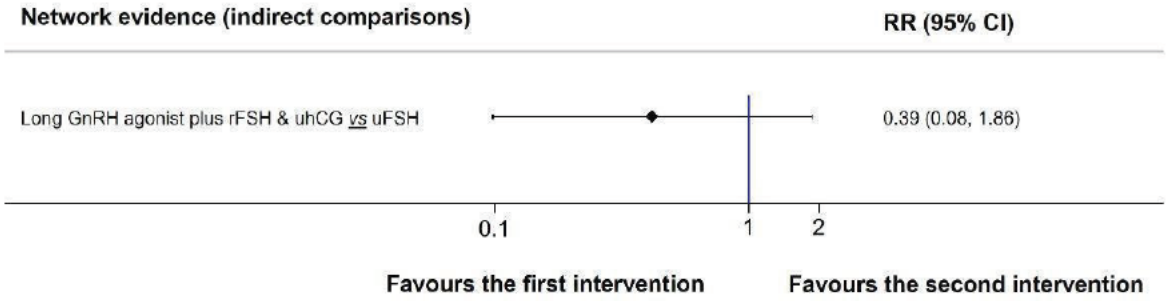
Figure 49 shows the network diagram for multiple pregnancy in women with predicted high response undergoing long GnRH agonist protocols. The network was connected. There were two direct comparisons and one indirect comparison. The evidence is very uncertain for all d rect (An lys 6.5 and Analysis 14.4) and indirect (Figure 50) estimate

Figure 49. Network diagram of long GnRH agonist protocols for the ou come of multiple pregnancy in women with predicted high response. The nodes represent an intervention a d their si e is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) a d their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. Th colour of the line is red for very low-certainty evidence.



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Figure 50. Forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of multiple pregnancy in women with predicted high response.



Other networks - short GnRH antagonist protocols; GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of multiple pregnancy in women with predicted high response.

5.3. Women with predicted LOW response

Pituitary suppression methods

There was only one comparison between pituitary suppression methods for the outcome of multiple pregnancy in women with predicted low response (short GnRH antagonist versus long GnRH agonist protocols).

Short GnRH antagonist versus long GnRH agonist

Short GnRH antagonis protoc ls may result in little to no difference in multiple pregnancy versus long GnRH agonist protocols (RR 0.44, 95% CI 0.11 to 1.6 1 study, 394 women; low-certainty evidence; nalysis 1.5)

6. Misca riage

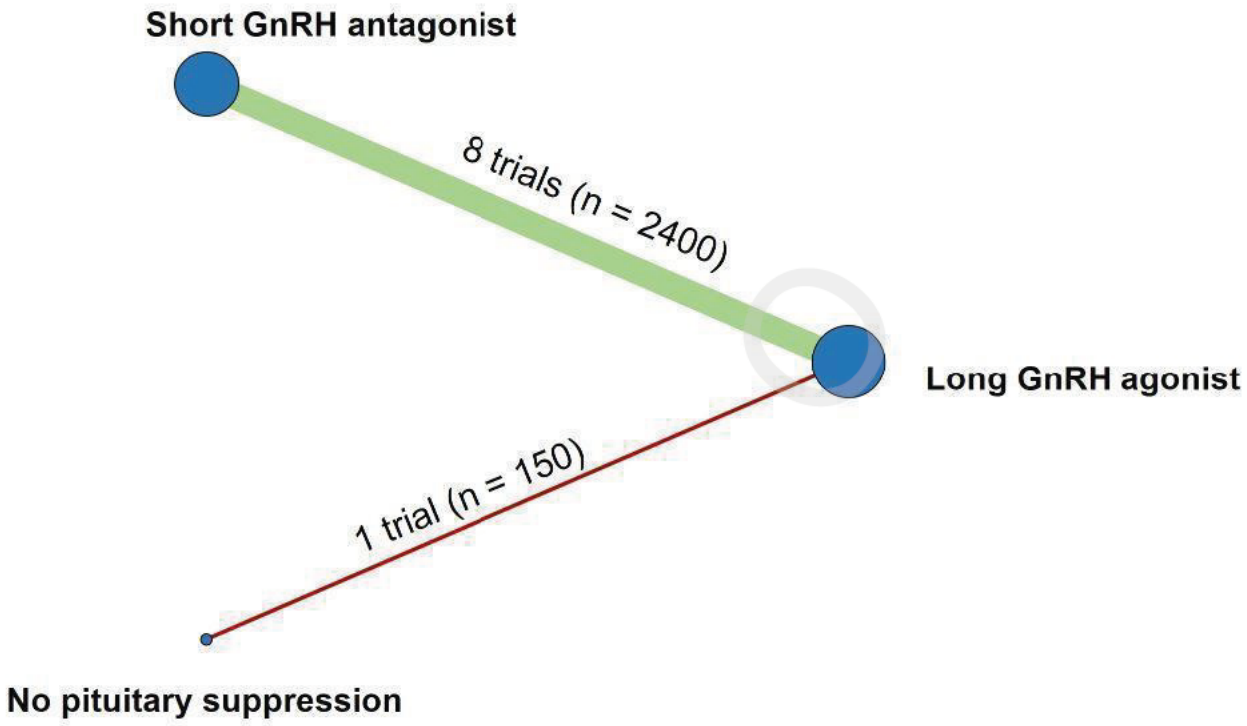
6.1. Women with predicted NORMAL response

Pituitary suppression methods

igure 51 shows the network diagram of pituitary suppression methods for the outcome of miscarriage in women with predicted normal response. The network was connected. There were two direct comparisons and one indirect comparison.

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Figure 51. Network diagram of pituitary suppression methods for the outcome of miscarriage in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

Short GnRH antagonist versus long GnRH agonist

Short antagonist protocols probably re ul in litt no difference in miscarriage rate versus long agonis proto ols (RR 0.95, 95% CI 0.73 to 1.24, 8 studies, 2400 women, I^2 = 0%; moderate-certainty evidence; Analysis 1.6).

No pituitary suppression versus long GnRH agonist

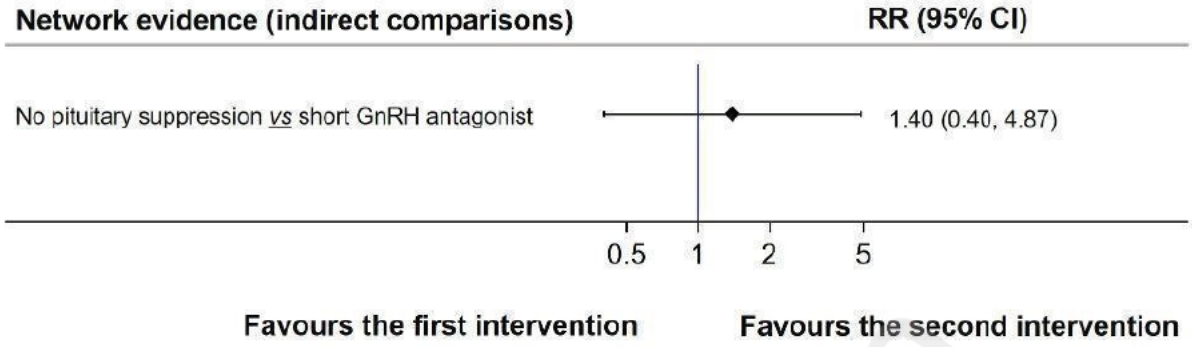
The evidence is very uncertain about this comparison (RR 1.33, 95% CI 0.39 to 4.51, 1 study, 150 women; very low-certainty evidence; Analysis 3.4).

Network estimates (indirect evidence only)

For the remaining indirect comparison, the network evidence is very uncertain (for effect estimates, see Figure 52).

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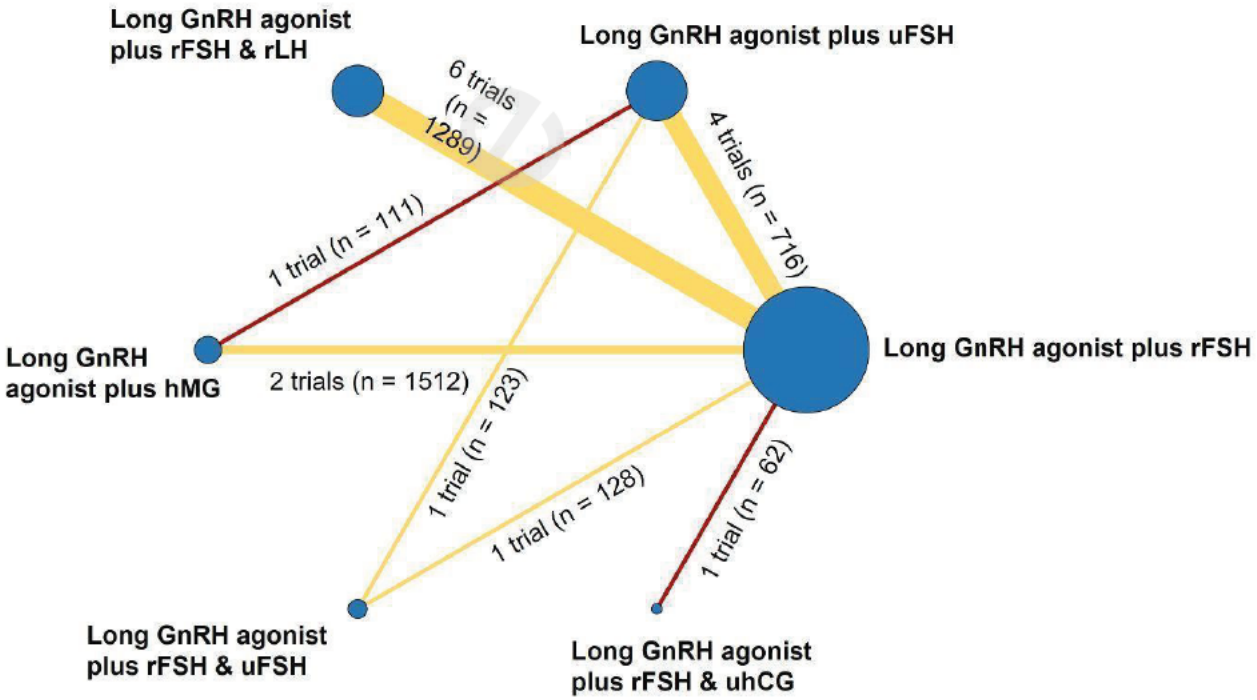
Figure 52. Forest plot comparing pituitary suppression methods with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparison) for the outcome of miscarriage in women with predicted normal response.



Long GnRH agonist protocols

Figure 53 shows the network diagram for miscarriage in women with predicted normal response undergoing long GnRH agonist protocols. The network was connected. There were two comparisons for which only direct evidence was available; five comparisons for which both direct and indirect evidence were available; and eight indirect comparisons evaluated through network meta-analysis.

Figure 53. Network diagram of long GnRH agonist protocols for the outcome of miscarriage in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparisons

rFSH & rLH versus rFSH

Combined rFSH and rLH may result in little to no difference in miscarriage rate versus rFSH (RR 0.88, 95% CI 0.56 to 1.40, 6 studies, 1289 women, I^2 = 0%; low-certainty evidence; Analysis 10.6).

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rFSH & uhCG versus rFSH

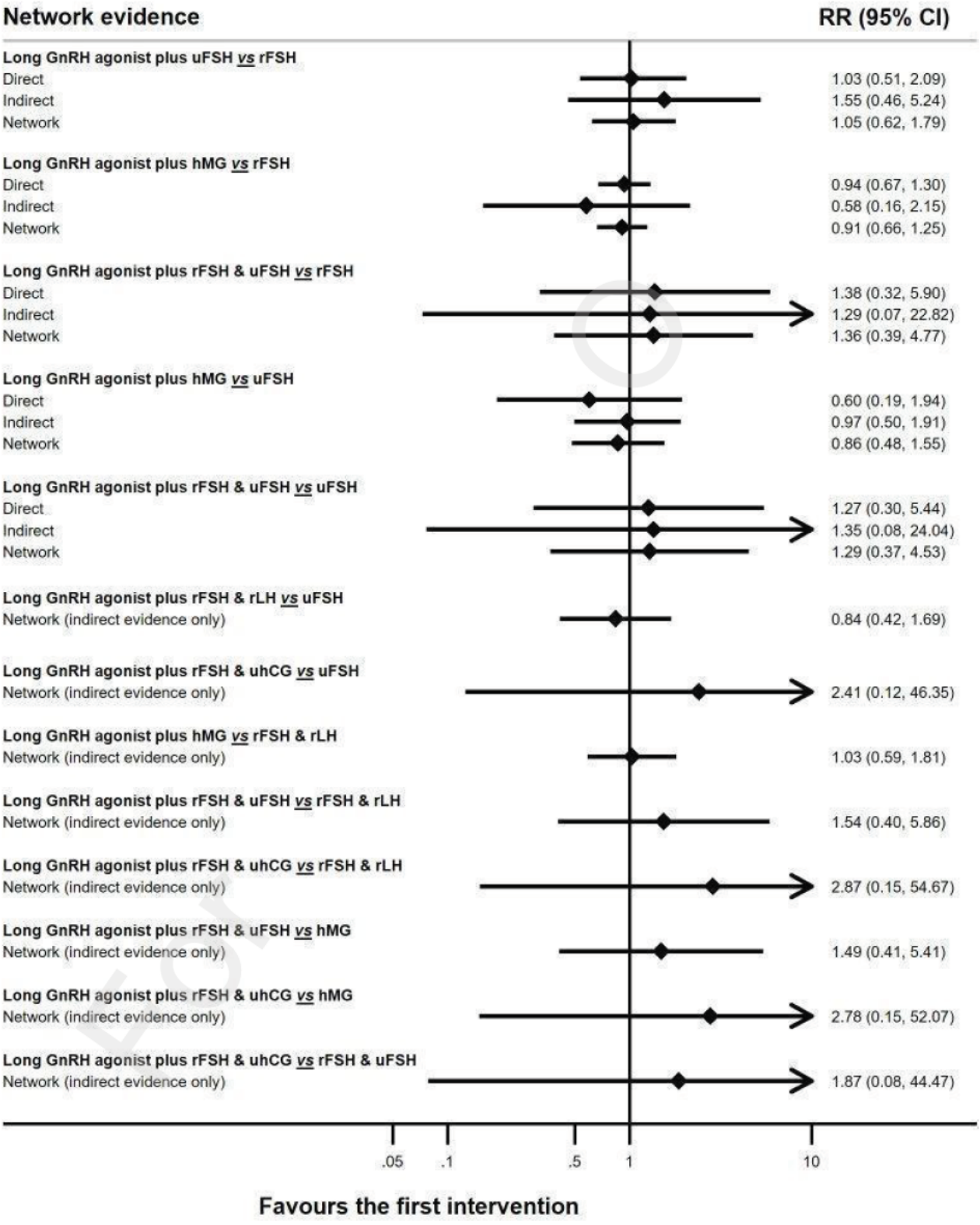
The evidence is very uncertain about this comparison (RR 2.53, 95% CI 0.14 to 46.52, 1 study, 62 women; very low-certainty evidence; Analysis 14.5).

Network estimates

For the thirteen remaining comparisons, the network evidence is either uncertain or very uncertain (for effect estimates, see Figure 54).

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Figure 54. Forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (direct, indirect and network estimates; where no RCTs were conducted for a specific comparison, only the indirect [network] estimate is presented) for the outcome of miscarriage in women with predicted normal response.

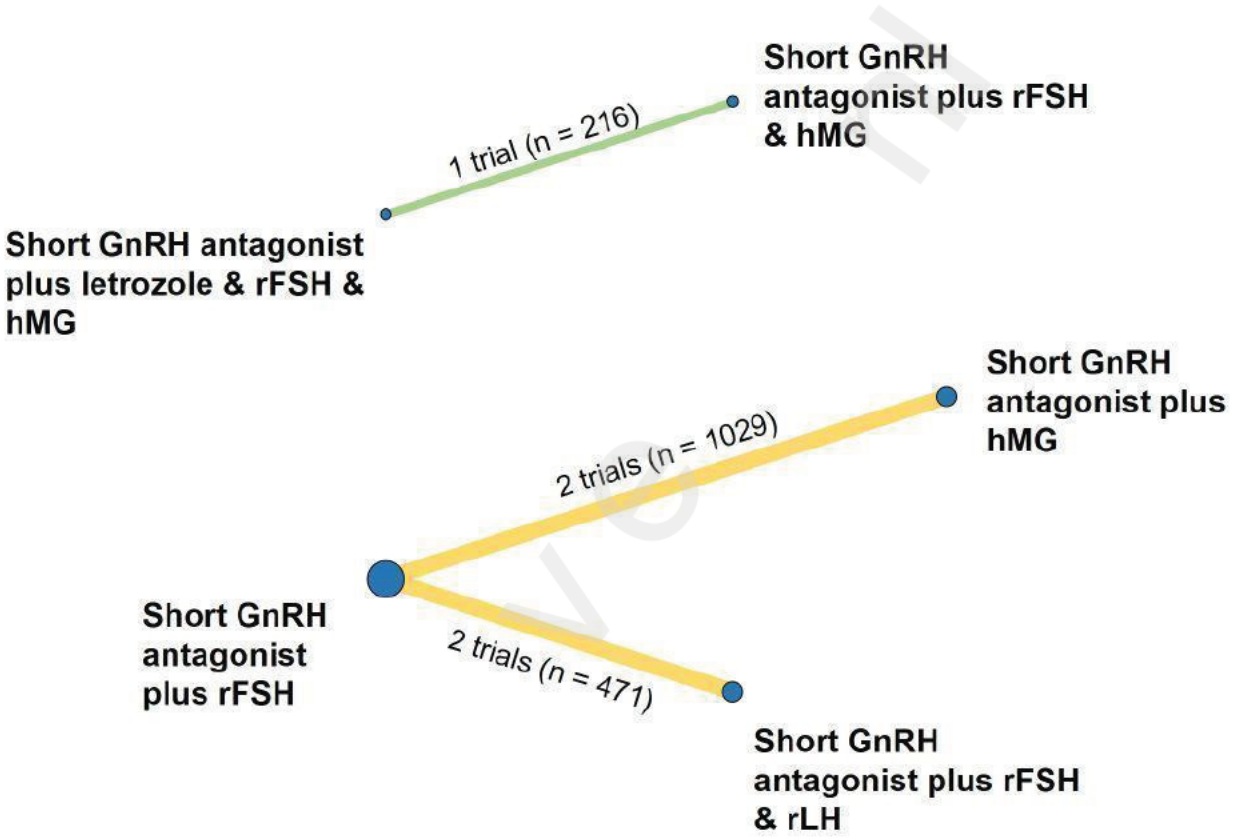


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Short GnRH antagonist protocols

Figure 55 shows the network diagram for miscarriage in women with predicted normal response undergoing short GnRH antagonist protocols. The network was disconnected. There were three direct comparisons and one indirect comparison.

Figure 55. Network diagram of short GnRH antagonist protocols for the outcome of miscarriage in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence and amber for low-certainty evidence.



Direct comparisons

hMG versus rFSH

Human menopausal gonadotrop in may result in little to no difference in miscarriage ve sus rFSH (RR 1.07, 95% CI 0.73 to 1.58, 2 studies, 1029 women, I^2 = 0 low-certainty evidence; Analysis 17.6).

rFSH & rLH versus rFSH

Combined rFSH and rLH may result in little to no difference in miscarriage rate versus rFSH (RR 1.06, 95% CI 0.50 to 2.28, 2 studies, 471 women, I^2 = 0%; low-certainty evidence; Analysis 18.5).

Letrozole, hMG & rFSH versus hMG & rFSH

Combined letrozole, hMG and rFSH probably reduces miscarriage rate versus hMG and rFSH (RR 0.05, 95% CI 0 to 0.86, 1 study, 216 women; moderate-certainty evidence; Analysis 27.2).

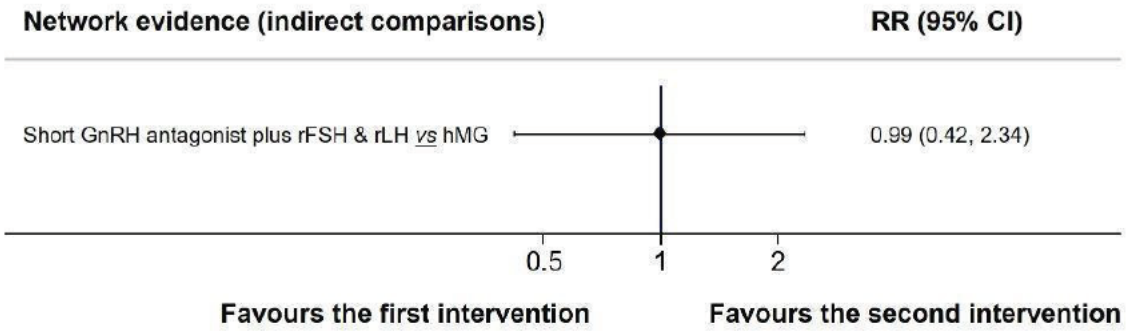
Network estimates (indirect evidence only)

Short GnRH antagonist plus rFSH & rLH versus hMG

Combined rFSH and rLH may result in little to no difference in miscarriage versus hMG (RR 0.99, 95% CI 0.42 to 2.34; low-certainty evidence; Figure 56).

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Figure 56. Forest plot comparing short GnRH antagonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons) for the outcome of miscarriage in women with predicted normal response.



Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of miscarriage in women with predicted normal response.

6.2. Women with predicted HIGH response

Pituitary suppression methods

There was only one direct comparison between pituitary suppression methods for the outcome of miscarriage in women with predicted high response (short GnRH antagonist versus long GnRH agoni t).

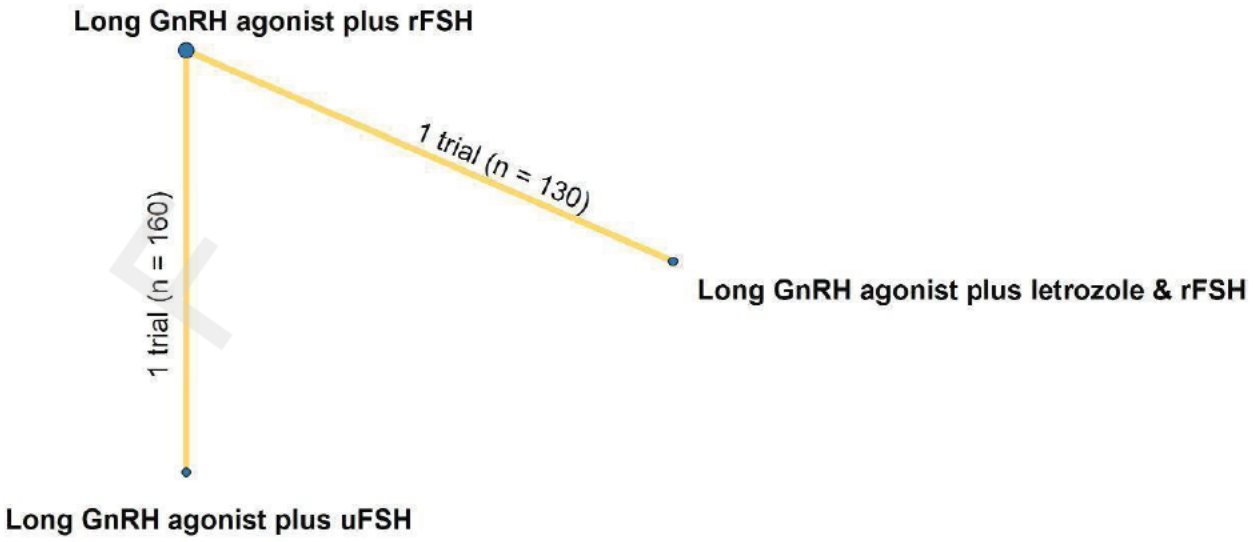
Short GnRH antagonist ersus long GnRH agonist

Short antagoni protocols may result in little to no difference in miscarriage versus long agonist protocols (RR 0.89, 95% CI 0.44 to 1.76, 2 studies, 356 women, I^2 = 0%; low-certainty evi nce; Analysis 1.6).

L ng GnRH agonist protocols

F gure 57 shows the network diagram for miscarriage in women with predicted high response undergoing long GnRH agonist pro ocols. The network was connected. There were two direct comparisons and one indirect comparison.

Figure 57. Network diagram of long GnRH agonist pro ocols for the outcome of miscarriage in women with predicted high response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised o trol ed trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluat d within each comparison. The colour of the line is amber for low-certainty evidence.



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Direct comparisons

uFSH versus rFSH

Urinary FSH may result in little to no difference in miscarriage rate versus rFSH (RR 0.78, 95% CI 0.30 to 1.99, 1 study, 160 women; low-certainty evidence; Analysis 6.6).

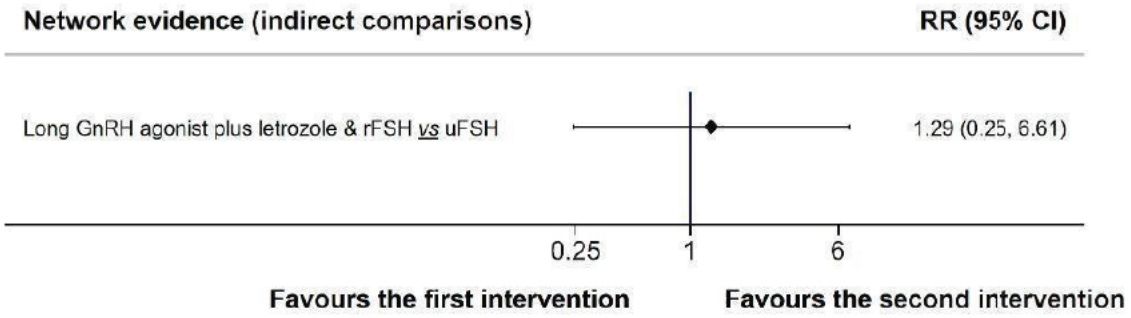
Letrozole & rFSH versus rFSH

Combined letrozole and rFSH may result in little to no difference in miscarriage rate versus rFSH (RR 1.00, 95% CI 0.26 to 3.83, 1 study, 130 women; low-certainty evidence; Analysis 9.4).

Network estimates (indirect evidence only)

For the seventeen remaining indirect comparisons, the network evidence is uncertain (for effect estimates, see Figure 58).

Figure 58. Forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of miscarriage in women with predicted high response.



Short GnRH antagonist protocols

There was only one direct comparison for miscarriage in women with predicted high response undergoing short GnRH antagonis protocols.

hMG versus rFSH

Human menopausal gonadotrophin may result in little to no difference in miscarriage rate versus rFSH (RR 0.62, 95% I 0.35 to 1.09, 1 study, 619 women; low-certainty evidence; A aly is 1 .6).

Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimu tion w thout pituitary suppression

The primary analysis did not includ a y studies comparing interventions within these networks for the utcome of miscarriage in women with predicted high response.

6.3. Women with predicted LOW sponse

Pituitary suppression methods

There was only one di ect comparison between pituitary suppression metho s for the out ome of miscarriage in women with predicted low resp nse (short GnRH antagonist versus long GnRH agonist proto ol).

Short GnRH antagonist versus long GnRH agonist

ho t antagonist protocols may result in little to no difference in miscarriage rate versus long agonist protocols (RR 1.16, 95% Ci 0.60 to 2.23, 3 studies, 1155 women, I^2 = 0%; low-certainty evidence; Analysis 1.6).

Long GnRH agonist protocols

There was only one direct comparison for miscarriage in women with predicted low response undergoing long GnRH agonist protocols (rFSH & rLH versus rFSH).

rFSH & rLH versus rFSH

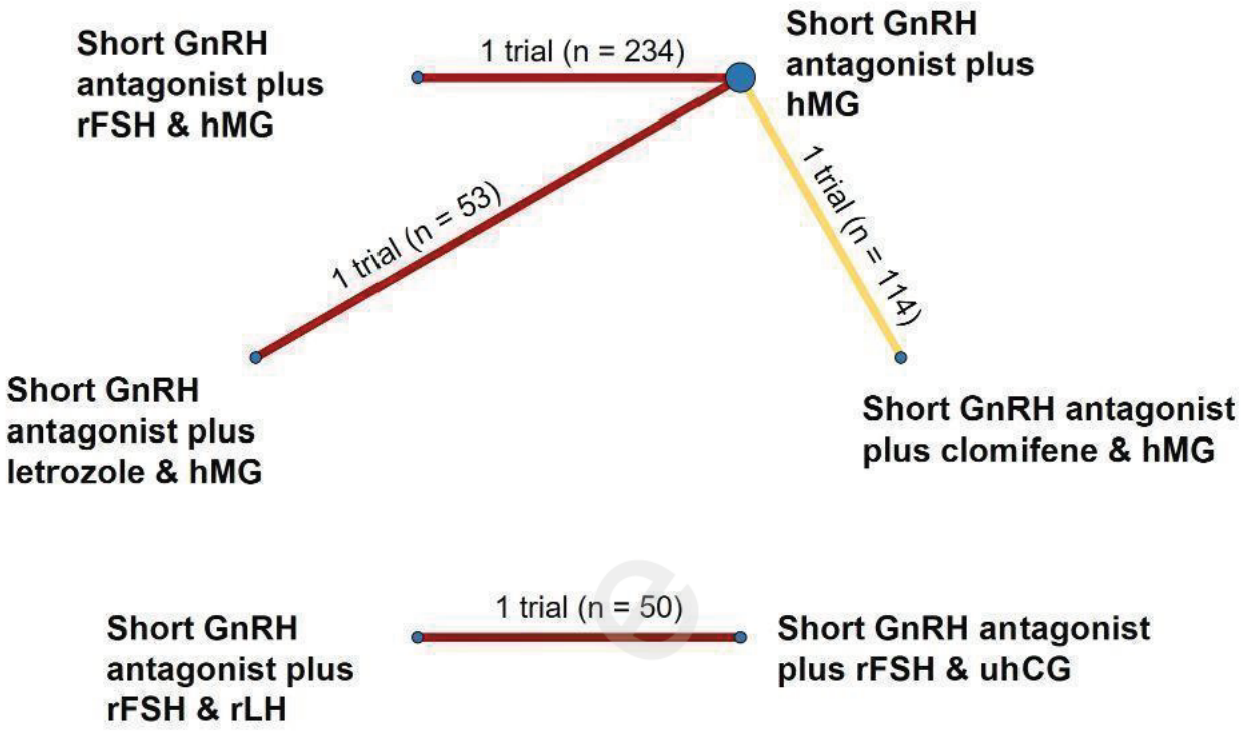
Combined rFSH and rLH probably reduce miscarriage rate versus rFSH (RR 0.60, 95% CI 0.42 to 0.85, 3 studies, 1313 women, I^2 = 0%; moderate-certainty evidence; Analysis 10.6).

Short GnRH antagonist protocols

Figure 59 shows the network diagram for miscarriage in women with predicted low response undergoing short GnRH antagonist protocols. The network was disconnected. There were four direct comparisons and three indirect comparisons.

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Figure 59. Network diagram of short GnRH antagonist protocols for the outcome of miscarriage in women with predicted low response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparisons

rFSH & hMG versus hMG

The evidence is very uncertain about his compar son (RR 1.20, 95% CI 0.38 to 3.82, 1 study, 234 women very low-certainty evidence; Analysis 18.5).

rFSH & uhCG versus rFSH & rLH

The evidence is very uncertain about this comparison (RR 0.33, 95% CI 0.01 to 7.81, 1 study, 50 women; very low-certainty evidence; Analysis 22.3).

Clomifene & hMG vers s hMG

Combined clomifene with hMG may result in little to no difference in miscarriage versus hMG (RR 0.67, 95% CI 0.20 to 2.24, 1 study, 114 women; low-certainty evidence; Analysis 24.2).

Letrozole & hMG versus hMG

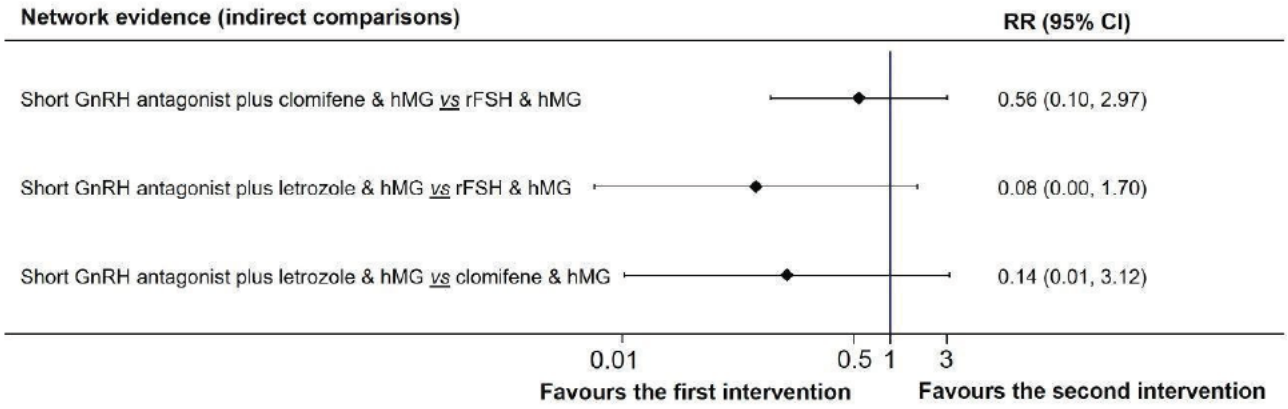
The evidence is very uncertain about this comparison (RR 0.09, 95% CI 0.01 to 1.62, 1 study, 53 women; very low-certainty evidence; Analysis 25.3).

Network estimates (indirect evidence only)

For the three remaining indirect comparisons, the network evidence is very uncertain (for effect estimates, see Figure 60).

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Figure 60. Forest plot comparing short GnRH antagonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of miscarriage in women with predicted low response.



Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of miscarriage in women with predicted low response.

7. Ectopic pregnancy

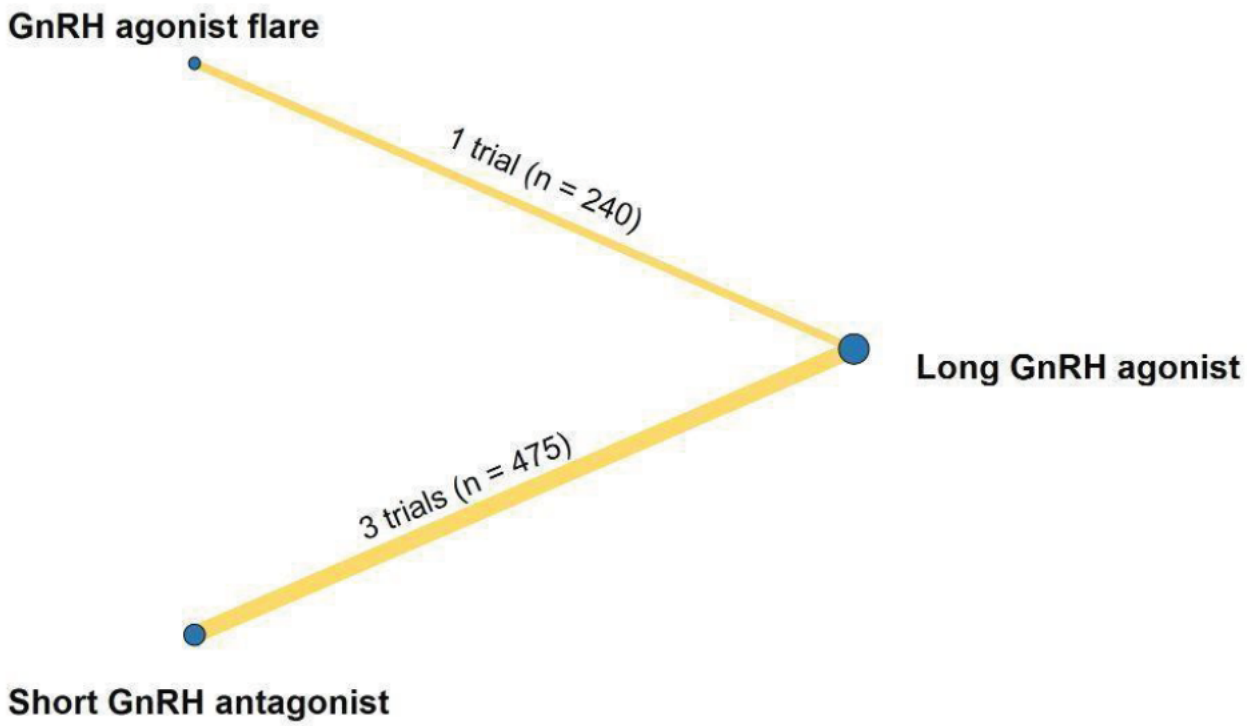
7.1. Women with predicted NORMAL response

Pituitary suppression methods

Figure 61 shows the network diagram of pituitary suppression methods for the outcome of ectopic pregnancy in women with predicted normal response. The network was connected. There were two direct comparisons and one indirect comparison.

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Figure 61. Network diagram of pituitary suppression methods for the outcome of ectopic pregnancy in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence.



Direct comparisons

Short GnRH antagonist versus long GnRH agonist

Short antagonist protocols may result in little to no difference in ectopic pregnancy versus long agonist protocols (RR 1.14, 95% CI 0.14 to 9.20, 3 studies, 475 women, I^2 = 0%; low-certainty evidence; Analysis 1.7).

GnRH agonist flare versus long GnRH agonist

GnRH agonist flare protocols may result in little to no difference in ectopic pregnancy versus long GnRH agonist protocols (RR 2.50, 95% CI 0.49 to 12.64, 1 study, 240 women; low-certainty evidence; Analysis 2.4).

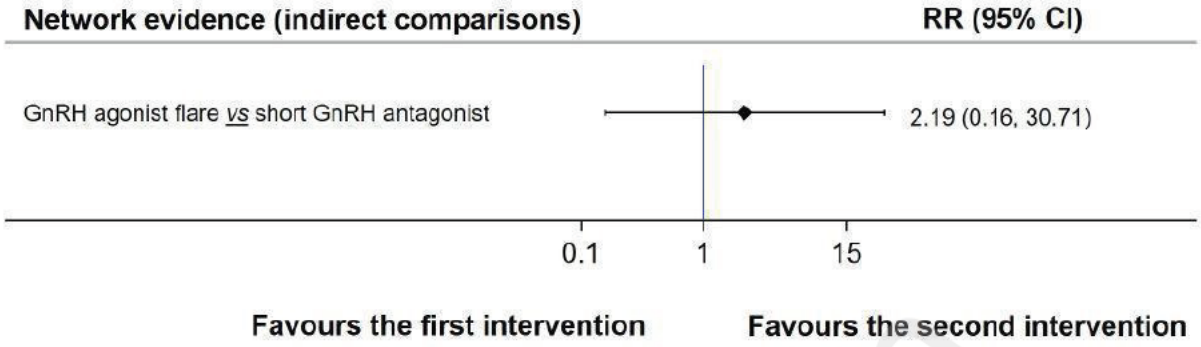
Network estimates (indirect evidence only)

GnRH agonist flare versus short GnRH antagonist

GnRH agonist flare protocols may result in little to no difference in ectopic pregnancy versus short GnRH antagonist protocols (RR 2.19, 95% CI 0.16 to 30.71; low-certainty evidence; Figure 62).

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Figure 62. Forest plot comparing pituitary suppression methods with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of ectopic pregnancy in women with predicted normal response.

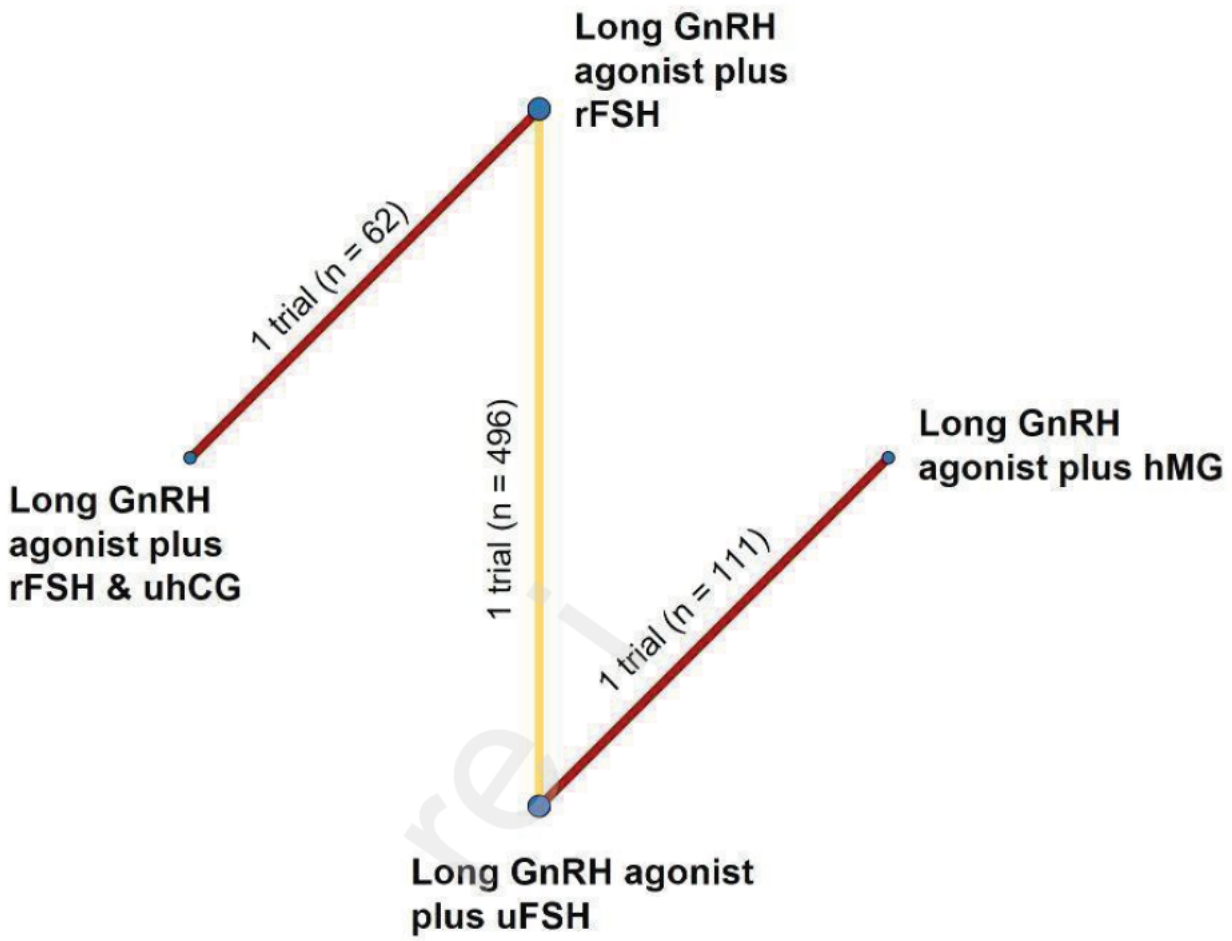


Long GnRH agonist protocols

Figure 63 shows the network diagram for ectopic pregnancy in women with predicted normal response undergoing long GnRH agonist protocols. The network was connected. There were three direct comparisons and three indirect comparisons.

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Figure 63. Network diagram of long GnRH agonist protocols for the outcome of ectopic pregnancy in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparisons

uFSH versus rFSH

Urinary FSH may result in little to no difference in ectopic pregnancy versus rFSH (RR 1.98 95% CI 18 to 21.74, 1 study, 496 women; low-certainty evidence Analysis 6.7).

hMG versus uFSH

The evidence is very uncertain about this comparison (RR 0.15, 95% CI 0.01 to 2.85, 1 study, 111 women; very low-certainty evidence; Analysis 8.4).

rFSH & uhCG versus rFSH

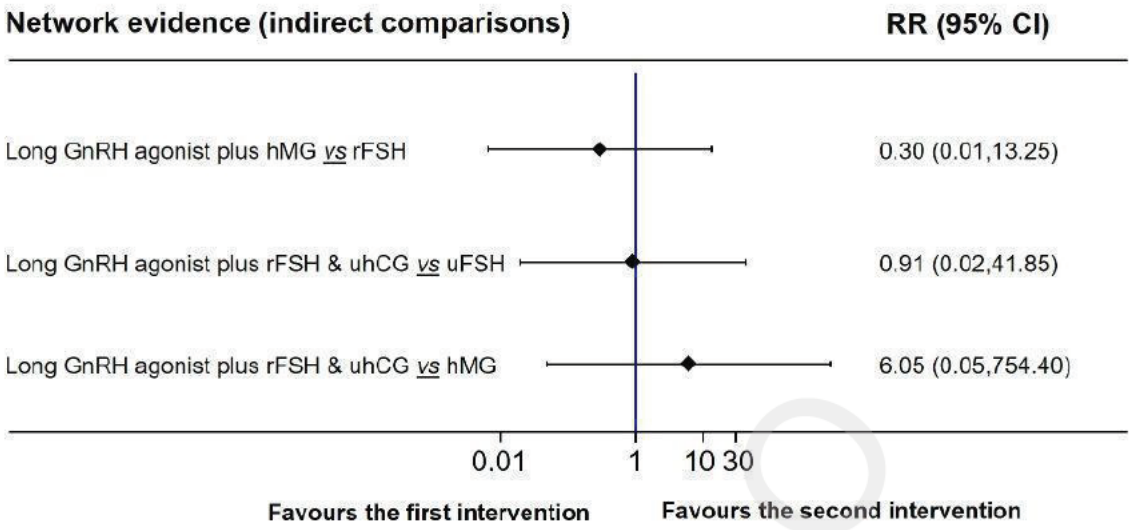
The evidence is very uncertain about this comparison (RR 1.81, 95% CI 0.09 to 35.79, 1 study, 62 women; very low-certainty evidence; Analysis 14.6).

Network estimates (indirect evidence only)

For the three remaining indirect comparisons, the network evidence is very uncertain (for effect estimates, see Figure 64).

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Figure 64. Forest plot comparing long GnRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of ectopic pregnancy in women with predicted normal response.



Short GnRH antagonist protocols

There was only one direct comparison for ectopic pregnancy in women with predicted normal response undergoing short GnRH antagonist protocols (rFSH & rLH versus rFSH).

rFSH & rLH versus rFSH

Combined rFSH and rLH may result in little to no difference ectopic pregnancy versus rFSH (RR 0.77, 95% CI 0.21 to 2. 5, 2 studies, 471 women, I^2 = 0%; low-certainty evidence; Analysis 18 6).

Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation wi hou pit itary suppression

The primary analysis did not include any s dies comparing interventions within these networks f r the outco e of ectopic pregnancy in women with predicted normal r sponse.

7.2. Women with predicted HIGH respons

None of the trials included in the quantitative synthesis investigated the outcome of ectopic pregnancy in women with predicted high response.

7.3. Women with predicted LOW response

Pituitary suppression methods

There was only one direct comparison between pituitary suppression method for the outcome of ectopic pregnancy in women with predicted lo response (short GnRH antagonist versus long GnRH agonist protocols).

Short GnRH antagonist versus long GnRH agonist

The evidence is very uncertain about this comparison (RR 3.00, 95% CI 0.13 to 71.07, 1 study, 66 women; very low-certainty evidence; Analysis 1.7).

Long GnRH agonist protocols

There w s nly one direct comparison for ectopic pregnancy in women with predicted low response undergoing long GnRH agonist protocol (rFSH & rLH versus rFSH).

rFSH & rLH versus rFSH

Combined rFSH and rLH may result in little to no difference in ectopic pregnancy versus rFSH (RR 0.34, 95% CI 0.01 to 8.43, 1 study, 939 women; low-certainty evidence; Analysis 10.7).

Short GnRH antagonist protocols

There was only one comparison for ectopic pregnancy in women with predicted low response undergoing short GnRH antagonist protocols (rFSH & hMG versus hMG).

rFSH & hMG versus hMG

The evidence is very uncertain about this comparison (RR not estimable, 1 study, 234 women; very low-certainty evidence; Analysis 20.6).

Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of ectopic pregnancy in women with predicted low response.

8. Cancellation

8.1. Women with predicted NORMAL response

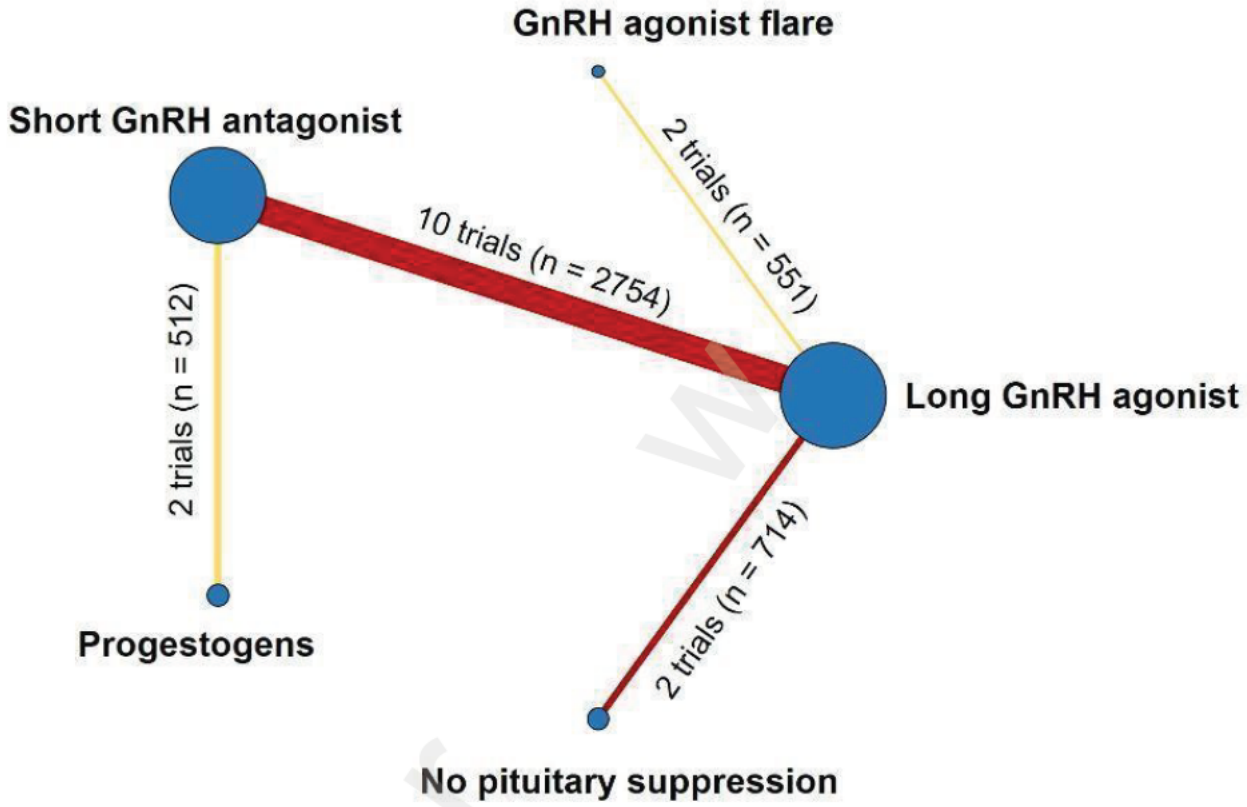
Pituitary suppression methods

Figure 65 shows the network diagram of pituitary suppression methods for the outcome of cancellation in women with predicted

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normal response. The network was connected. There were four direct comparisons and six indirect comparisons.

Figure 65. Network diagram of pituitary suppression methods for the outcome of cancellation in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparisons

Short GnRH antagonist versus long GnRH agoni t

The evidence is very uncertain about this comparison (RR 0.62, 95% CI 0.32 to 1.21, 10 studies 2754, I^2 = 72%; very low-certainty evidence; Analysis 1.8).

GnRH agonist flare v sus long GnRH agonist

GnRH agonist fla protocols may result in little to no difference in cancellation versus lo g GnRH agonist protocols (RR 1.53, 95% CI 0.46 to 5.07, 2 studies, 551 women; low-certainty evidence; Analysis 2.5).

No pituitary suppression versus long GnRH agonist

The evidence is very uncertain about this comparison (RR 0.67, 95% CI 0.13 to 3.35, 2 studies, 714 women, I^2 = 87%; very low-certainty evidence; Analysis 3.5).

Progestogen versus short GnRH antagonist

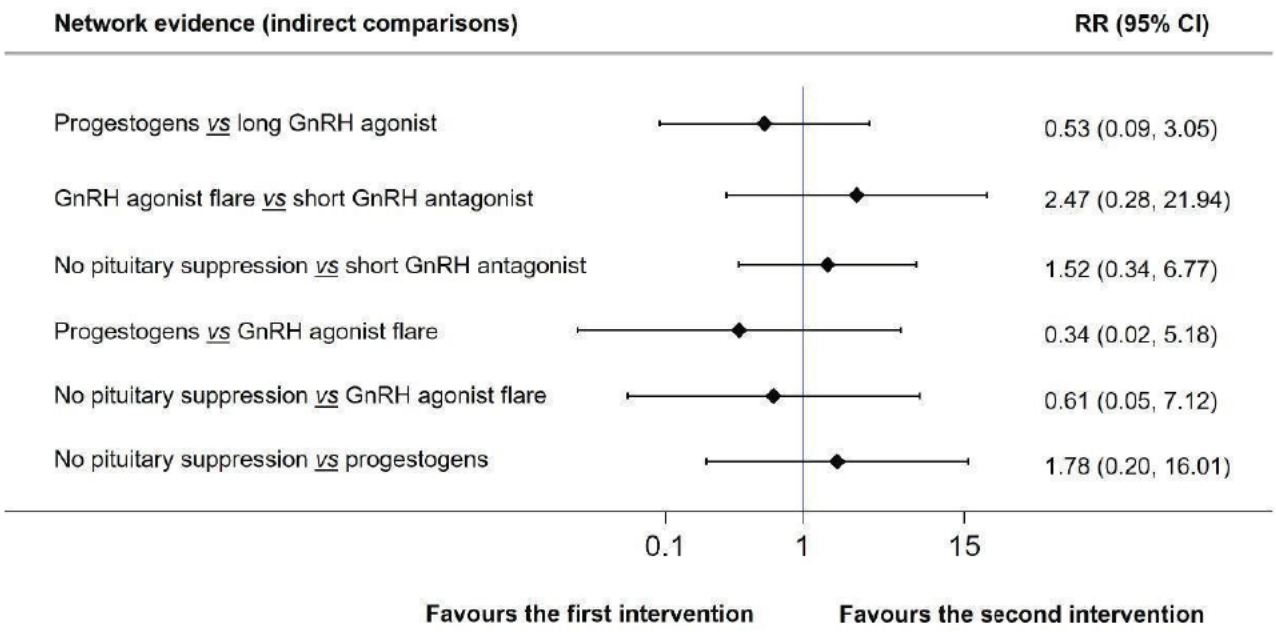
Pituitary suppression with progestogens may result in little to no difference in cancellation versus short GnRH antagonist protocols (RR 0.85, 95% CI 0.29 to 2.49, 2 studies, 512 women; I^2 = 0%; low-certainty evidence; Analysis 5.1).

Network evidence (indirect evidence only)

For the six remaining indirect comparisons, the network evidence is very uncertain (for effect estimates, see Figure 66).

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Figure 66. Forest plot comparing pituitary suppression methods with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of cancellation in women with predicted normal response.

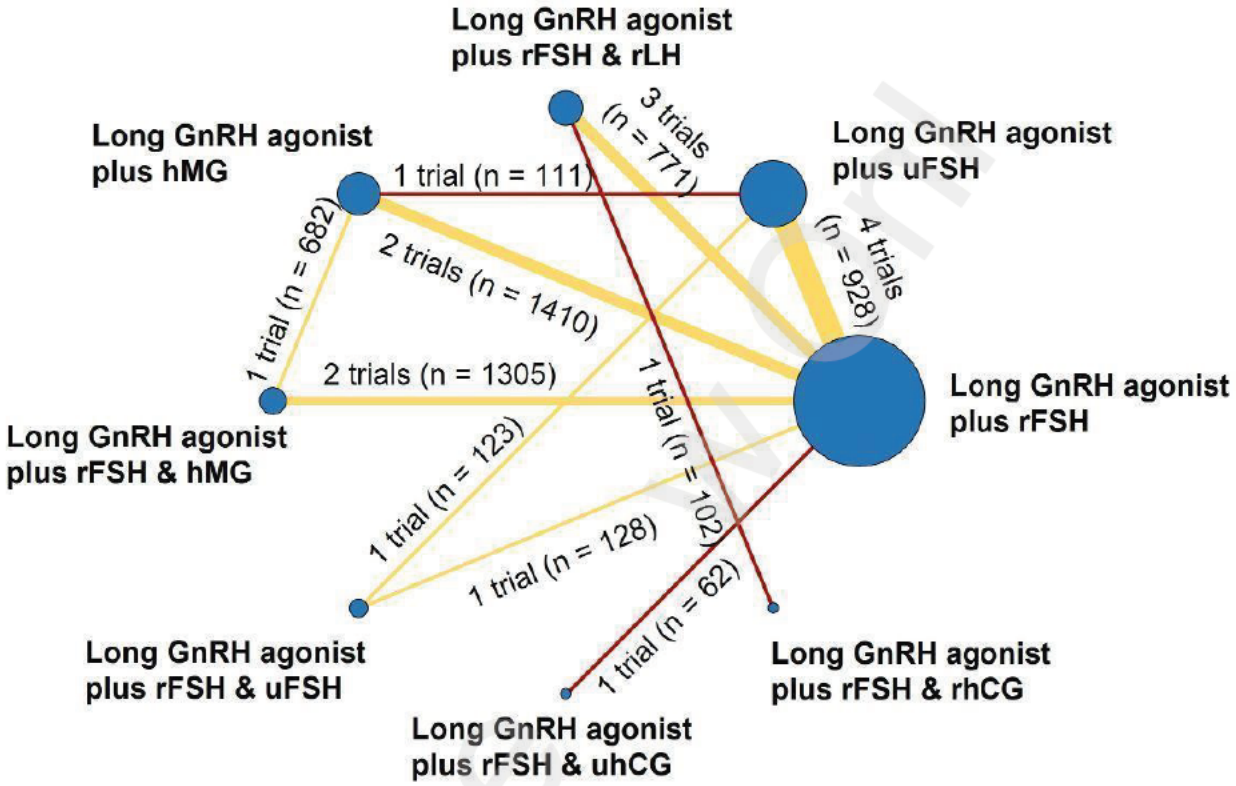


Long GnRH agonist protocols

Figure 67 presents the network diagram for cancellation i women with predicted normal response undergoing long GnRH agonist protocols. The network was connected. There were th ee compa ons for which only direct evidence was available; seven comparisons for which both direct and indirect evidence were ava able; and eighteen indirect comparisons evaluated through network meta-analysis.

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Figure 67. Network diagram of long GnRH agonist protocols for the outcome of cancellation in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.

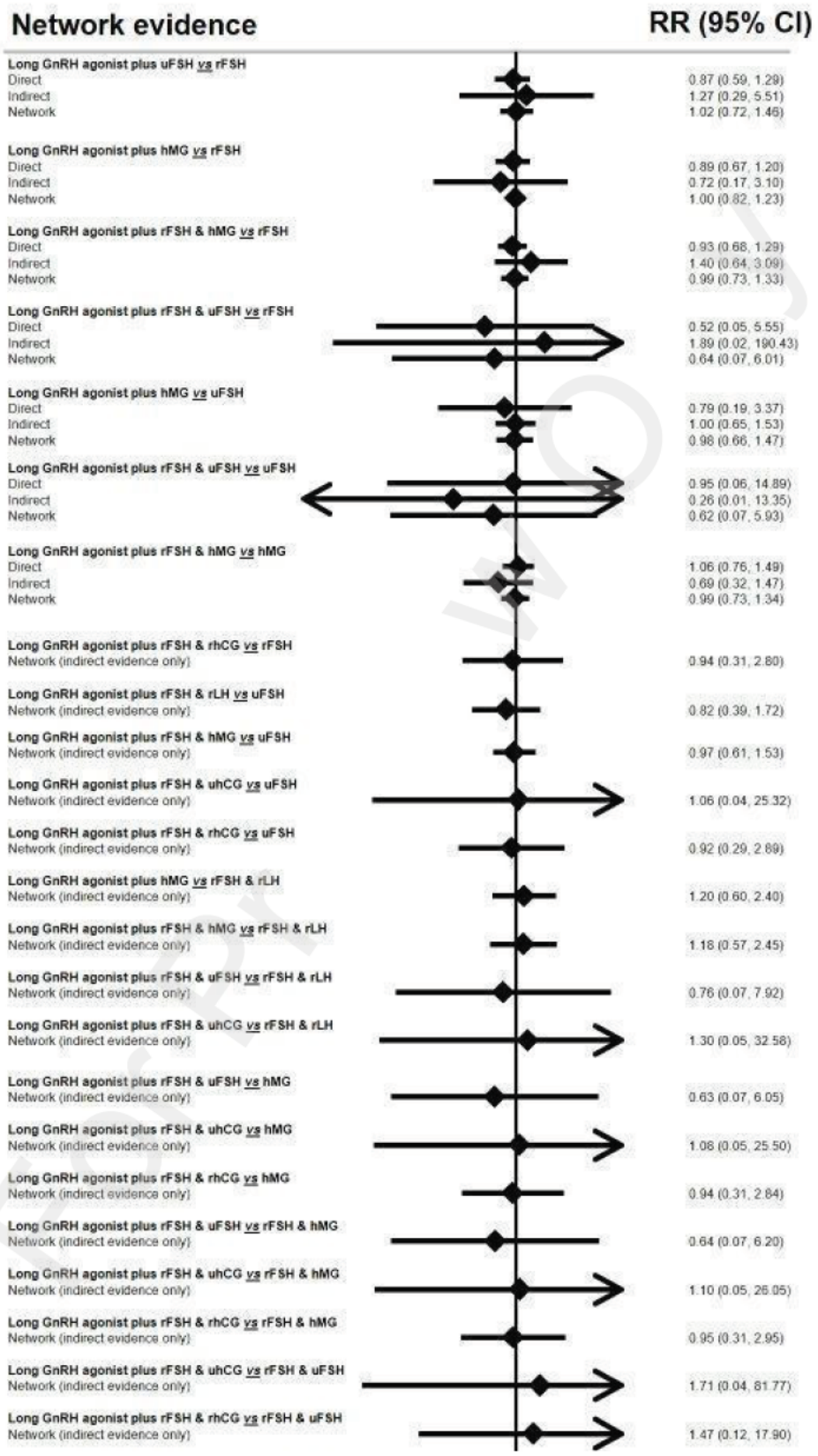


The network evidence is either uncert in r very uncertain (for effect estimates of direct comparisons, see nalysis 6.8; Analysis 7.7; Analysis 8.5; Analysis 10.8; Analysi 11.3 Analysis 12.3; Analysis 13.4; Analysis 14.7; Analysis 15.5; and Analysis 16.2, for network evidence estimates, see Figure 68).

Figure 68. Forest plot comparing long nRH agonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (direct, indirect and network estimates; where no RCTs were conducted for a

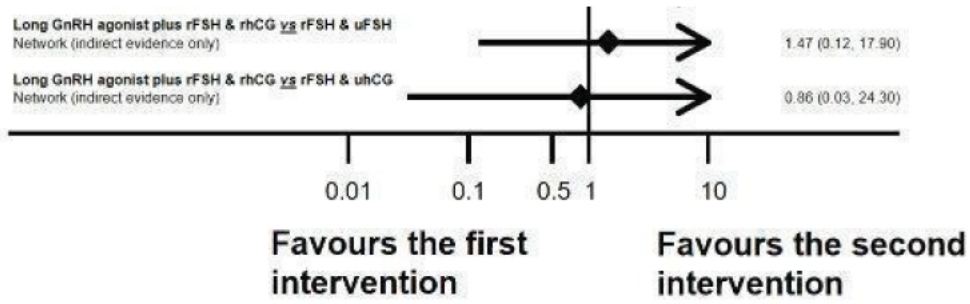
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specific comparison, only the indirect [network] estimate is presented) for the outcome of cancellation in women with predicted normal response.



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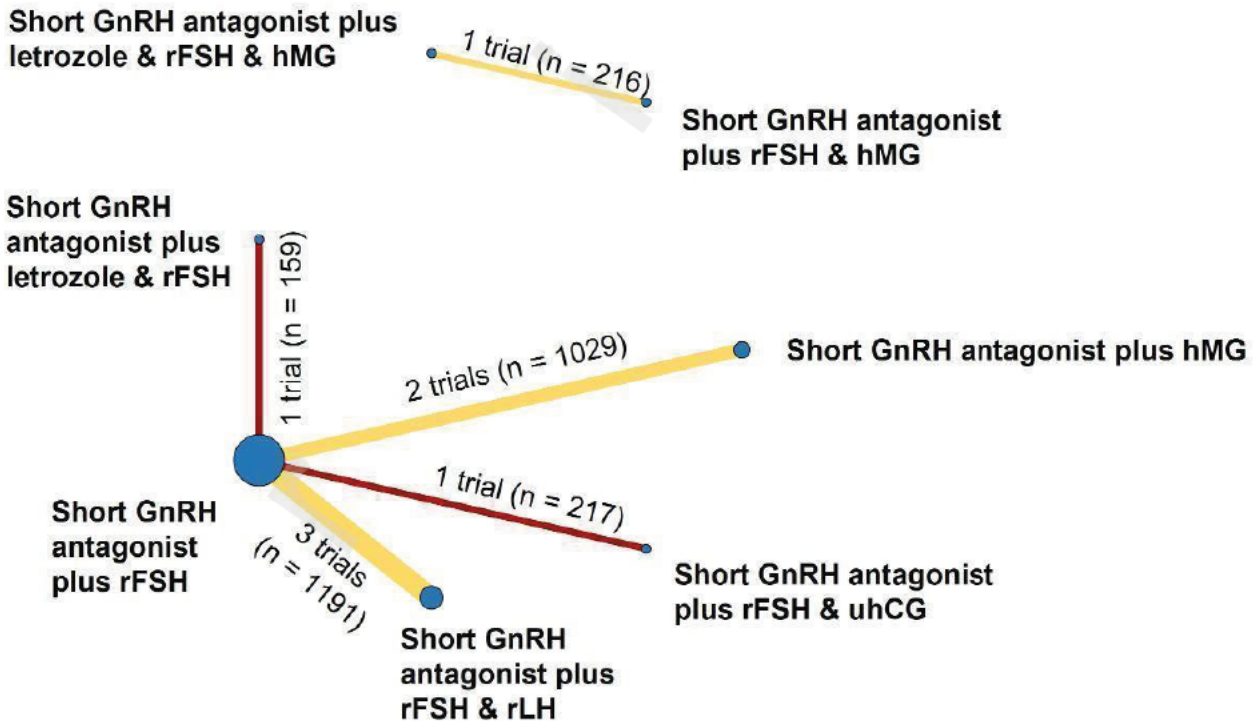
Figure 68. (Continued)



Short GnRH antagonist protocols

Figure 69 presents the network diagram for cancellation in women with predicted normal response undergoing short GnRH antagonist protocols. The network was c nnect d. There were five direct comparisons and six i direc comparisons.

Figure 69. Network diagram of short GnRH antagonist protocols for he outcome of cancellation in women with predicted normal response. The nodes represent an intervention and heir size s proportional to the number of trials comparing this intervention to any other in the network. The lines onnecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparisons

hMG versus rFSH

Human menopausal gonadotrophin may result in little to no difference in cancellation versus rFSH (RR 1.13, 95% CI 0.67 to 1.93, 2 studies, 1029 women, I^2 = 0%; low-certainty evidence; Analysis 17.7).

rFSH & rLH versus rFSH

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Combined rFSH and rLH may result in little to no difference in cancellation versus rFSH (RR 0.81, 95% CI 0.40 to 1.63, 3 studies, 1191 women, I^2 = 43%; low-certainty evidence; Analysis 18.7).

rFSH & uhCG versus rFSH

The evidence is very uncertain about this comparison (RR 0.73, 95% CI 0.17 to 3.18, 1 study, 217 women; very low-certainty evidence; Analysis 21.3).

Letrozole & rFSH versus rFSH

The evidence is very uncertain about this comparison (RR 0.59, 95% CI 0.15 to 2.40, 1 study, 159 women; very low-certainty evidence; Analysis 26.3).

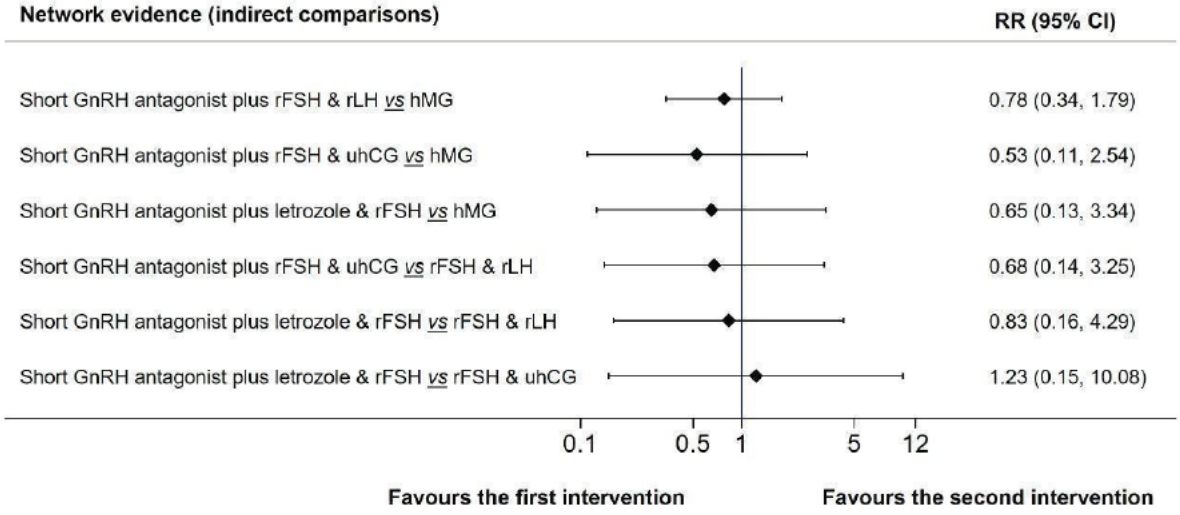
Letrozole, hMG & rFSH versus short rFSH & hMG

Combined letrozole, hMG and rFSH may result in little to no difference in cancellation versus hMG and rFSH (RR 0.22, 95% CI 0.01 to 4.43, 1 study, 216 women; low-certainty evidence; Analysis 27.4).

Network estimates (indirect evidence)

For the six remaining comparisons, the network evidence is either uncertain or very uncertain (for effe t estimates, see Figure 70).

Figure 70. Forest plot comparing short GnRH antagonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only for the ou come of cancellation in women with predicted normal response.



No pituitary suppression

There was only one direct comparison f p otoco using ovarian stimulation without pituitary suppr ssion or the outcome of cancellation in women with predic ed n rmal response (hMG versus uFSH).

hMG versus uFSH

The evidence is very uncertain ab ut this comparison (RR 1.16, 95% CI 0.29 to 4.70, 1 study, 158 women; very low-certainty evidence; Analysis 30.3).

Other networks - G RH agonis fl re protocols; and progestogens for pituita y suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of cancellation in women with predicted normal response.

8.2. Women with predicted HIGH response

Pituitary suppression methods

There was only one comparison between pituitary suppression methods for the outcome of cancellation in women with predicted high response (short GnRH antagonist versus long GnRH agonist).

Short GnRH antagonist versus long GnRH agonist

Short antagonist protocols may result in little to no difference in cancellation versus long agonist protocols (RR 1.42, 95% CI 0.76 to 2.66, 576 women, 3 studies, I^2 = 2%; low-certainty evidence; Analysis 1.8).

Long GnRH agonist protocols

There was only one direct comparison for cancellation in women with predicted high response undergoing long GnRH agonist protocols (uFSH versus rFSH).

uFSH versus rFSH

Urinary FSH may result in little to no difference in cancellation versus rFSH (RR 3.00, 95% CI 0.12 to 72.56, 1 study, 160 women; low-certainty evidence; Analysis 6.8).

Short GnRH antagonist protocols

There was only one direct comparison for cancellation in women with predicted high response undergoing short GnRH antagonist protocols (hMG versus rFSH).

hMG versus short rFSH

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Ovarian stimulation with hMG probably increases cancellation versus rFSH (RR 5.98, 95% CI 1.78 to 20.10, 1 study, 619 women; moderate-certainty evidence; Analysis 17.7).

Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

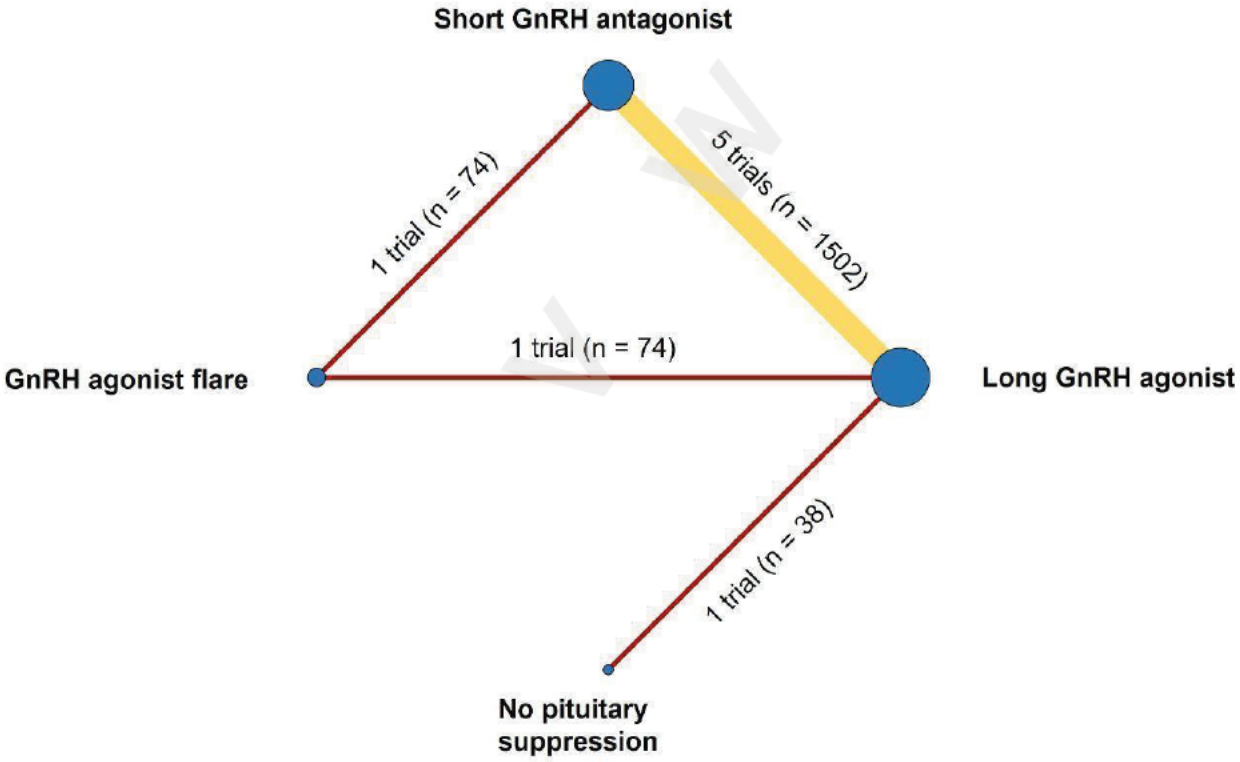
The primary analysis did not include any studies comparing interventions within these networks for the outcome of cancellation in women with predicted high response.

8.3. Women with predicted LOW response

Pituitary suppression methods

Figure 71 shows the network diagram of pituitary suppression methods for the outcome of cancellation in women with predicted low response. The network was connected. There was one comparison for which only direct evidence was available; three comparisons for which both direct and indirect evidence were available; and two indirect comparisons evaluated through network meta-analysis.

Figure 71. Network diagram of pituitary suppression methods for the outcome of cancellation in women with predicted low response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparison

No pituitary suppression versus long GnRH agonist

The evidence is very uncertain about this comparison (RR 1.92, 95% CI 0.13 to 28.32, 1 study, 38 women; very low-certainty evidence; Analysis 3.5).

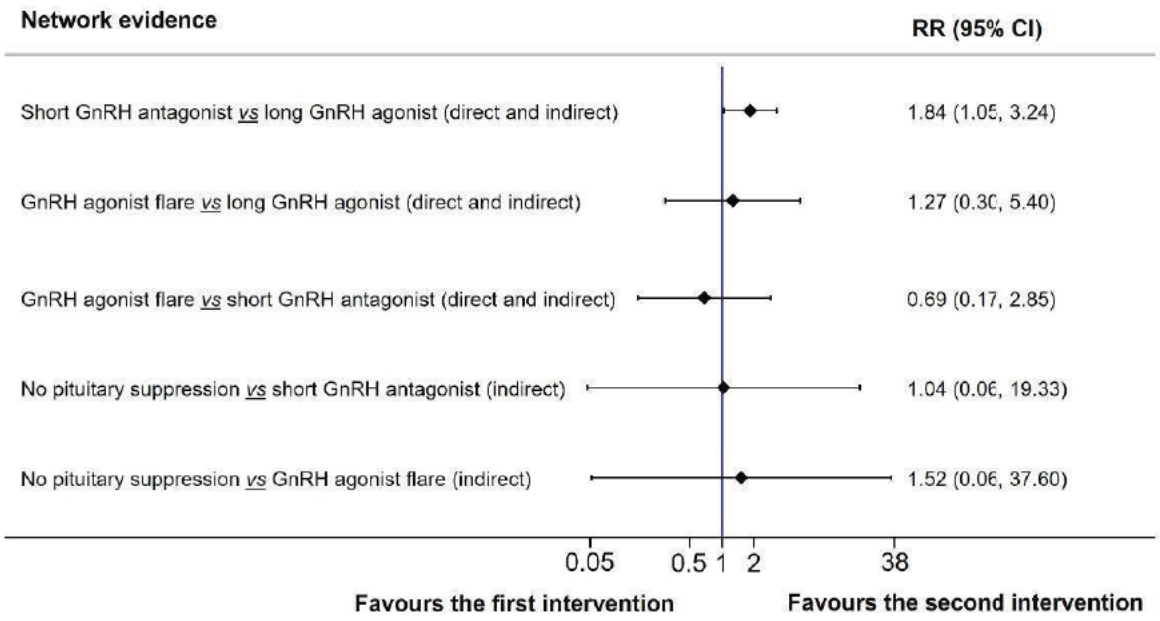
Network estimates (direct and indirect evidence)

Short GnRH antagonist versus long GnRH agonist (direct and indirect evidence)

Short GnRH antagonist protocols may increase cancellation versus long GnRH agonist protocols (RR 1.84, 95% CI 1.05 to 3.24; low-certainty evidence; Figure 72).

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Figure 72. Forest plot comparing pituitary suppression methods with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of cancellation in women with predicted low response.



GnRH agonist flare versus long GnRH agonist (direct and indirect evidence)

The evidence is very uncertain about this comparison (RR 1.27, 95% CI 0.30 to 5.40; very low-certainty evidence; Figure 72).

GnRH agonist flare versus short GnRH antagonist (direct and indi ect evidence)

The evidence is very uncertain about this comparison (RR .69, 95% CI 0.17 to 2.85; very low-certainty evidence; Figure 72).

Remaining indirect comparisons

For the two remaining indirect compar sons, t e network evidence is very uncertain (for effect estimates, see Figure 72).

Long GnRH agonist protocols

There was only one direct compa ison for cancellation in women with predicted low response dergoing long GnRH agonist protocols (rFSH & rLH versus rFSH).

rFSH & r H versus rFSH

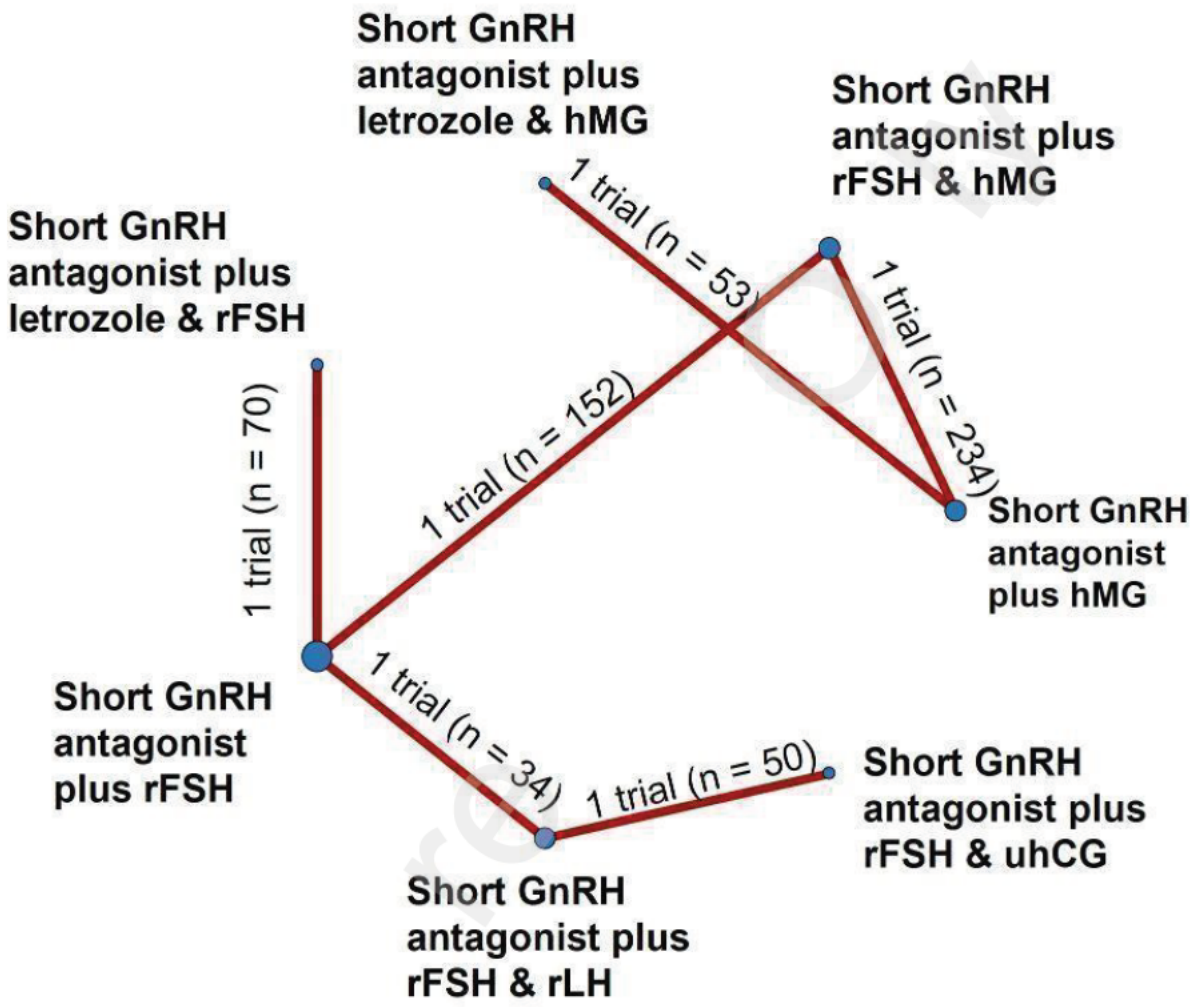
ombined rFSH and rLH may result in little to no difference in can ellation versus rFSH (RR 0.99, 95% 0.68 to 1.43, 3 studies, 1313 women, I2 = 0%; low-certainty evidence; Analysis 10.8).

Short GnRH antagonist protocols

Figure 73 presents the network diagram for cancellation in women with predicted low response undergoing short GnRH antagonist protocols. The network was connected. There were six direct comparisons and fifteen indirect comparisons. For all direct and indirect comparisons, the network evidence is very uncertain (very low-certainty evidence; for effect estimates of direct comparisons, see Analysis 18.7; Analysis 19.4; Analysis 20.7; Analysis 22.4; Analysis 25.4; and Analysis 26.3; for network estimates, see Figure 74).

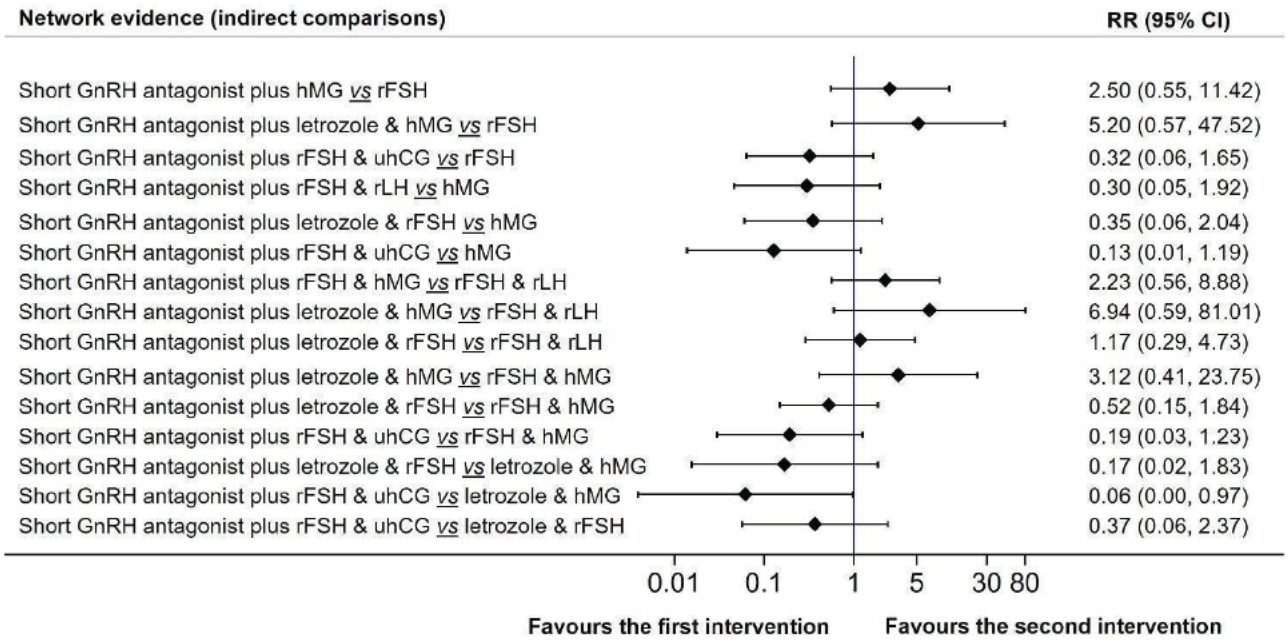
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Figure 73. Network diagram of short GnRH antagonist protocols for the outcome of cancellation in women with predicted low response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is red for very low-certainty evidence.



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Figure 74. Forest plot comparing short GnRH antagonist protocols with risk ratios (RR) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of cancellation in women with predicted low response.



GnRH agonist flare protocols

There was only one direct comparison for cancellation in wome with predicted low response undergoing GnRH agonist flare protocols (rFSH & rLH versus rFSH).

rFSH & rLH versus rFSH

Combined rFSH and rLH may result in little to no diff rence in cancellation versus rFSH (RR 1.00, 95% CI 0.27 to 3 74, 1 study, 84 women; low-certainty evidence; Analysis 28.1).

No pituitary suppression

There was only one direct compariso for ca cellation in women with predicted low response unde going ovarian stimulation without pituitary suppression (rFSH & hM versus uFSH & hMG).

FSH & hMG versus uFSH & hMG

The evidence is very uncertain about this comparison (RR 0.33, 95% CI 0.08 to 1.39, 1 study, 30 women; very low-certainty evidence; Analysis 29.1).

9. Oocyte number

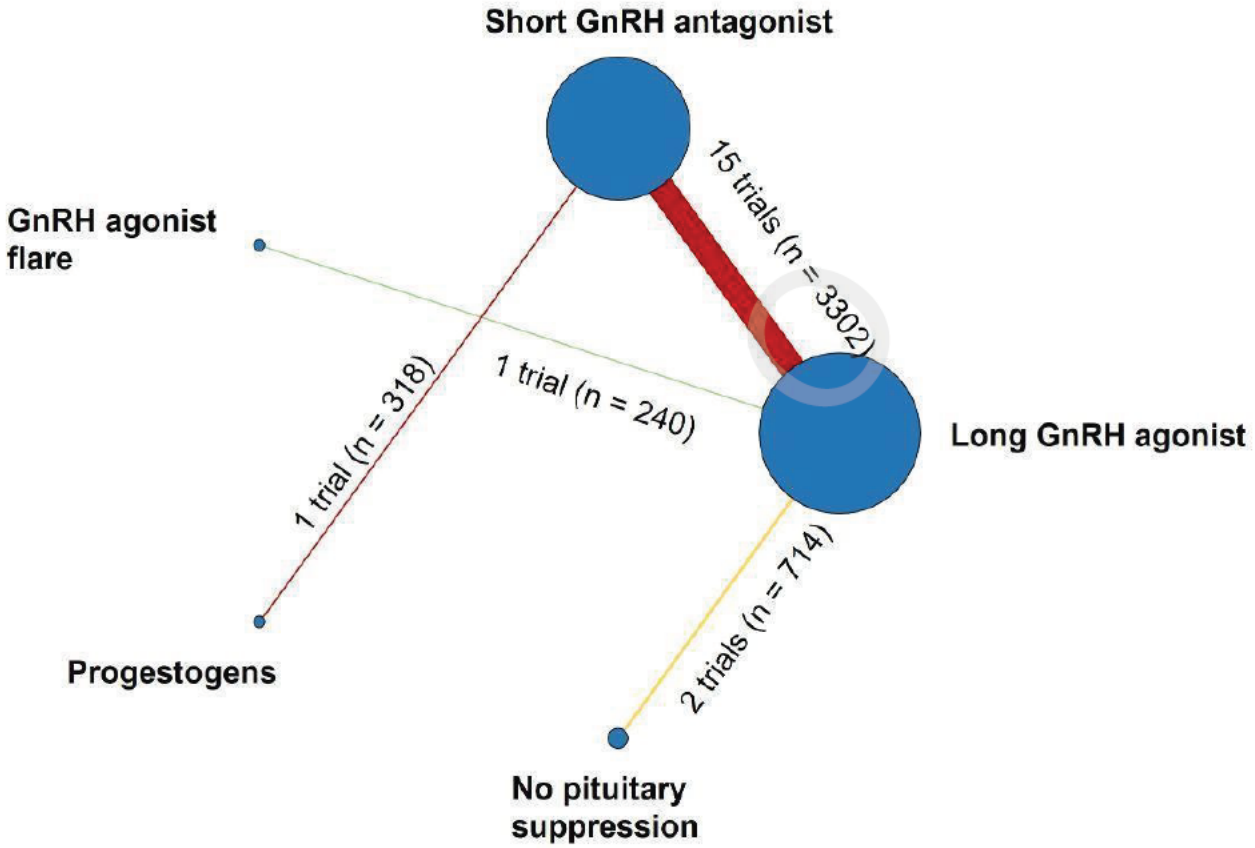
9.1. Women with predicted NORMAL response

Pituitary suppression methods

Figure 75 shows the network diagram of pituitary suppression methods for the outcome of oocyte number in women with predicted normal response. The network was connected. There were four direct comparisons and six indirect comparisons.

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Figure 75. Network diagram of pituitary suppression methods for the outcome of oocyte number in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

Short GnRH antagonist versus long GnRH ag nist

The evidence is very uncertain about this comparison (MD -0.71, 95% CI -1.75 to 0.33, 15 studies, 3 02 women, I^2 = 93%; very low-certainty evidence; Analysis 1.9).

GnRH agonist flare versus long GnR agonist

GnRH agonist flare protoco s probably reduce oocyte number versus long GnRH agonist protocols (MD -3.30, 95% CI -4.87 to -1.73, 1 study, 240 wome ; moderate-certainty evidence; Analysis 2.6).

No pituitary suppression ve sus long GnRH agonist

Ovarian stimulation without pituitary suppression may reduce oocyte number versus long GnRH agonist protocols (MD -5.80, 95% CI -11.24 to -0.36, 2 studies, 714 women; low-certainty evidence; Analysis 3.6).

Progestogen versus short GnRH antagonist

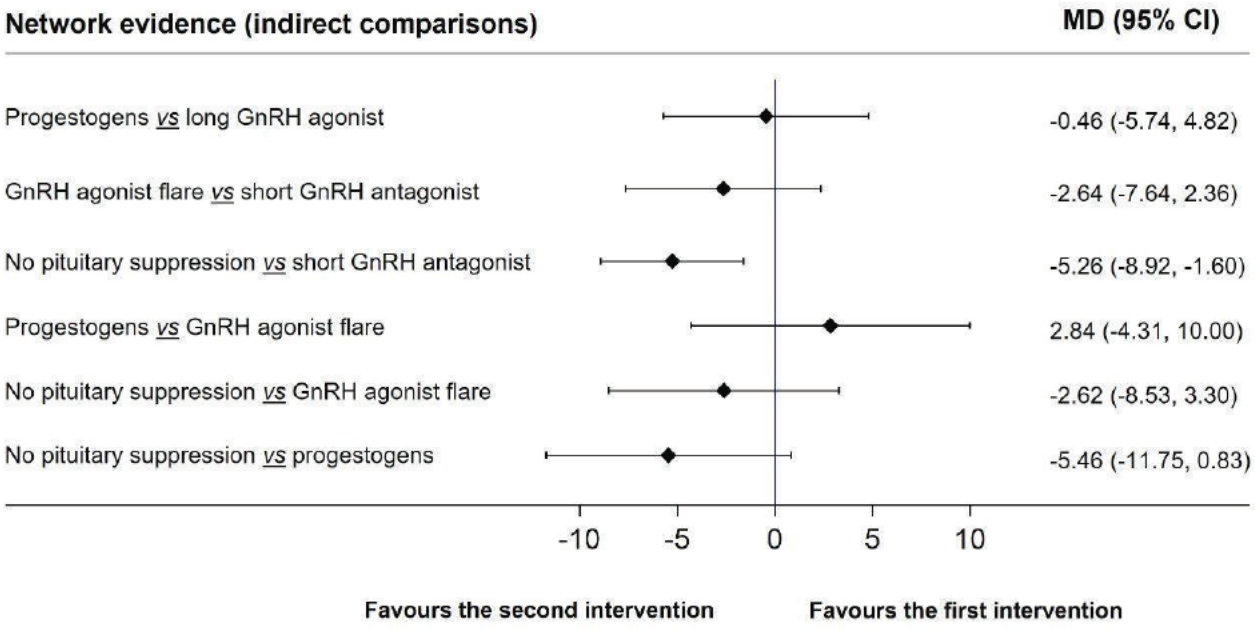
The evidence is very uncertain about this comparison (MD 0.20, 95% CI -2.11 to 2.51, 1 study, 318 women; very low-certainty evidence; Analysis 5.2).

Network estimates (indirect evidence only)

For the six remaining indirect comparisons, the network evidence is either uncertain or very uncertain (for effect estimates, see Figure 76).

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Figure 76. Forest plot comparing pituitary suppression methods with mean difference (MD) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of oocyte number in women with predicted normal response.

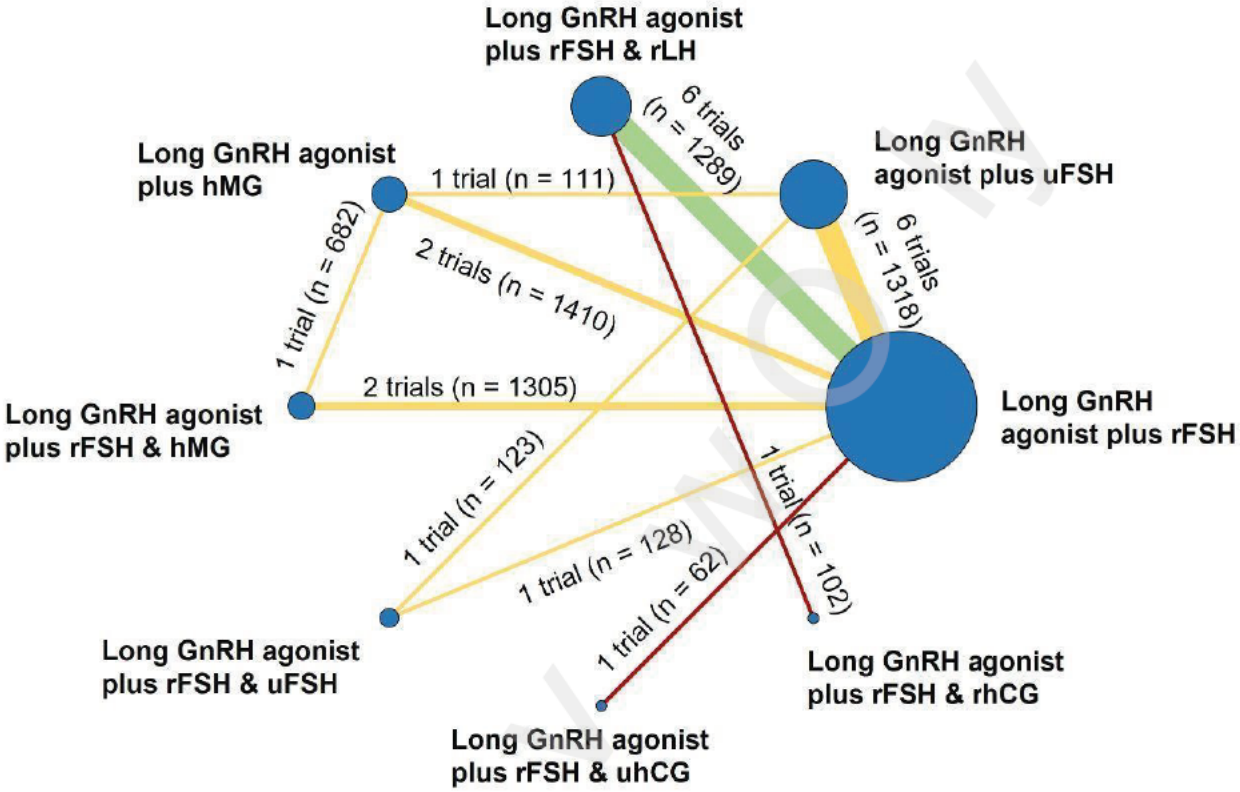


Long GnRH agonist protocols

Figure 77 presents the network diagram for oocyte number i women with predicted normal response undergoing long GnRH agonist protocols. The network was connected. There were th ee compa ons for which only direct evidence was available; seven comparisons for which both direct and indirect evidence were ava able; and eighteen indirect comparisons evaluated through network meta-analysis.

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Figure 77. Network diagram of long GnRH agonist protocols for the outcome of oocyte number in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

rFSH & rLH versus rFSH

Combined rFSH and rLH probably reduce ocyte number versus rFSH (MD -0.81, 95% CI -1.33 to -0.28, 6 tria s 1289 women, I^2 = 0%; moderate-certainty evidence; Analysis 10.9).

rFSH & rhCG versus rFSH & rLH

The evidence is very uncertain about this comparison (MD -0.80, 95% CI -2.55 to 0.95, 1 s udy, 10 women; very low-certainty evidence; Analysis 1 .5).

Long GnRH agonist plus rFSH & uhCG versus rFSH

The evidence is very uncertain about this comparison (MD 0.40, 95% CI -2.98 to 3.78, 1 study, 62 women; very low-certainty evidence; Analysis 14.8).

Network estimates

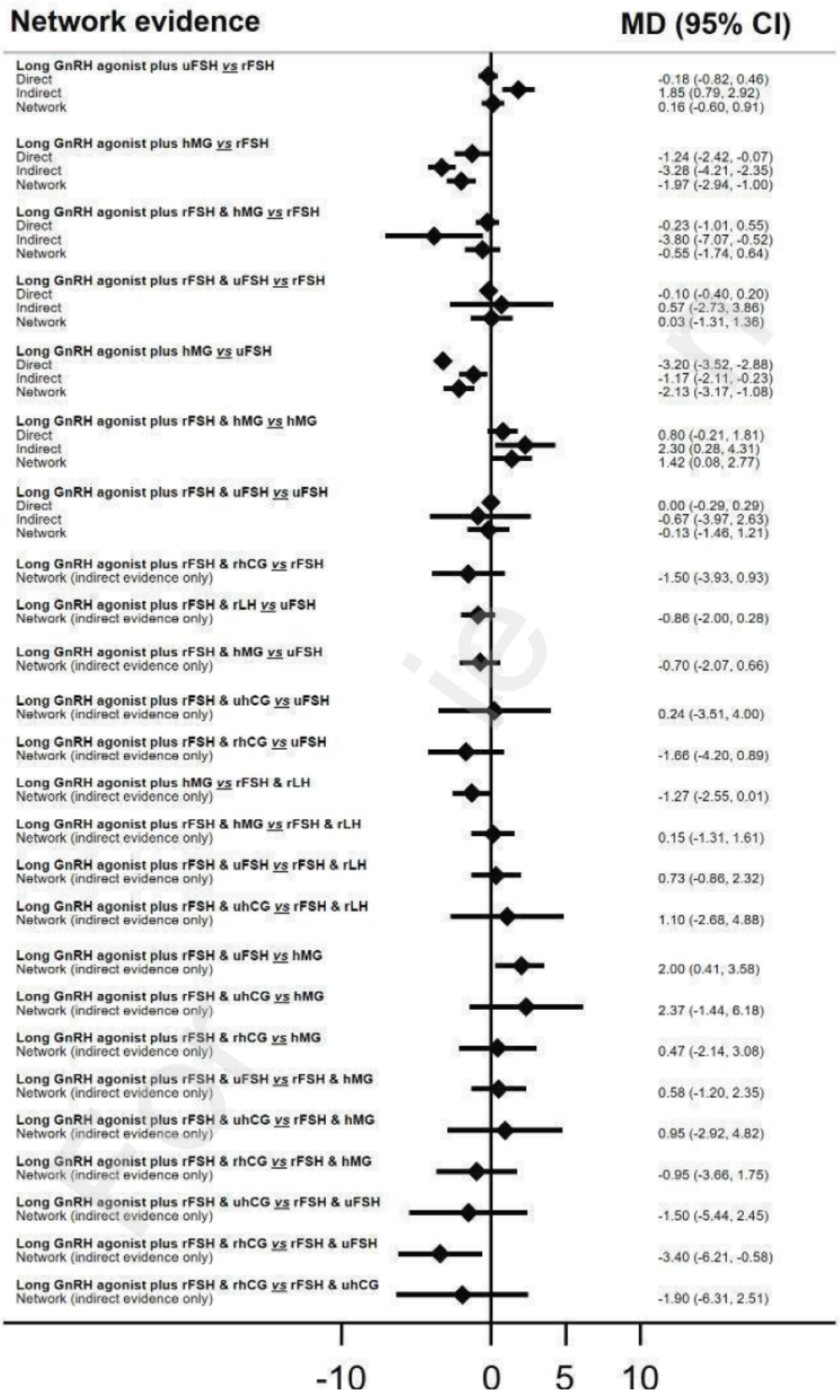
uFSH versus rFSH (direct and indirect evidence)

Urinary FSH may result in little to no difference in oocyte number versus rFSH (MD 0.16, 95% CI -0.60 to 0.91; low-certainty evidence; direct evidence: Analysis 6.9; network evidence: Figure 78).

Figure 78. Fore t plot comparing long GnRH agonist protocols with mean difference (MD) and 95% confidence intervals (CI) from n twork meta-analysis (direct, indirect and network estimates; where no RCTs were conducted

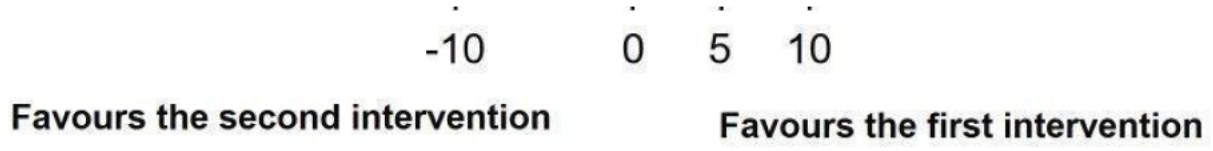
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for a specific comparison, only the indirect [network] estimate is presented) for the outcome of oocyte number in women with predicted normal response.



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Figure 78. (Continued)



hMG versus rFSH (direct and indirect evidence)

Human menopausal gonadotrophin may reduce oocyte number versus rFSH (MD -1.97, 95% CI -2.94 to -1.00; low-certainty evidence; direct evidence: Analysis 7.8; network evidence: Figure 78).

rFSH & hMG versus rFSH (direct and indirect evidence)

Combined hMG and rFSH may result in little to no difference in oocyte number versus rFSH (MD -0.55, 95% CI -1.74 to 0.64; low-certainty evidence; direct evidence: Analysis 15.6; network evidence: Figure 78).

rFSH & uFSH versus rFSH (direct and indirect evidence)

Combined rFSH and uFSH may result in little to no difference in oocyte number versus rFSH (MD 0.03, 95% CI -1.31 to 1.36; low-certainty evidence; direct evidence: Analysis 11.4; network evidence: Figure 78).

hMG versus uFSH (direct and indirect evidence)

Human menopausal gonadotrophin may reduce oocyte number versus uFSH (MD -2.13, 95% CI -3.17 to -1.08, 1 study, 111 wom n; low-certainty evidence; direct evidence: Analysis 8.6; ne work evidence: Figure 78).

rFSH & hMG versus hMG (direct and indirect evidence)

Combined rFSH and hMG may increase oocyte number versus hMG (MD 1.42, 95% CI 0.08 to 2 77; low-certainty evidence; direct evidence: Analysis 16.3; network e idence: Figure 78).

rFSH & uFSH versus uFSH (direct and direct evidence)

Combined rFSH and uFSH may result in little to no difference in oocyte number ve sus uFSH (MD -0.13, 95% CI -1.46 to 1.21; very low-certainty evid nce; direct evidence: Analysis 12.4; network evidence: Figure 78

rFSH & uFSH versus hM (indirect evidence only)

In women wit pred cted normal response undergoing long GnRH agonist protocols, combined rFSH and uFSH may increase oocyte numbe versus hMG (MD 2.00, 95% CI 0.41 to 3.58; low-certainty evidence; Figure 78).

Remai ing indirect comparisons

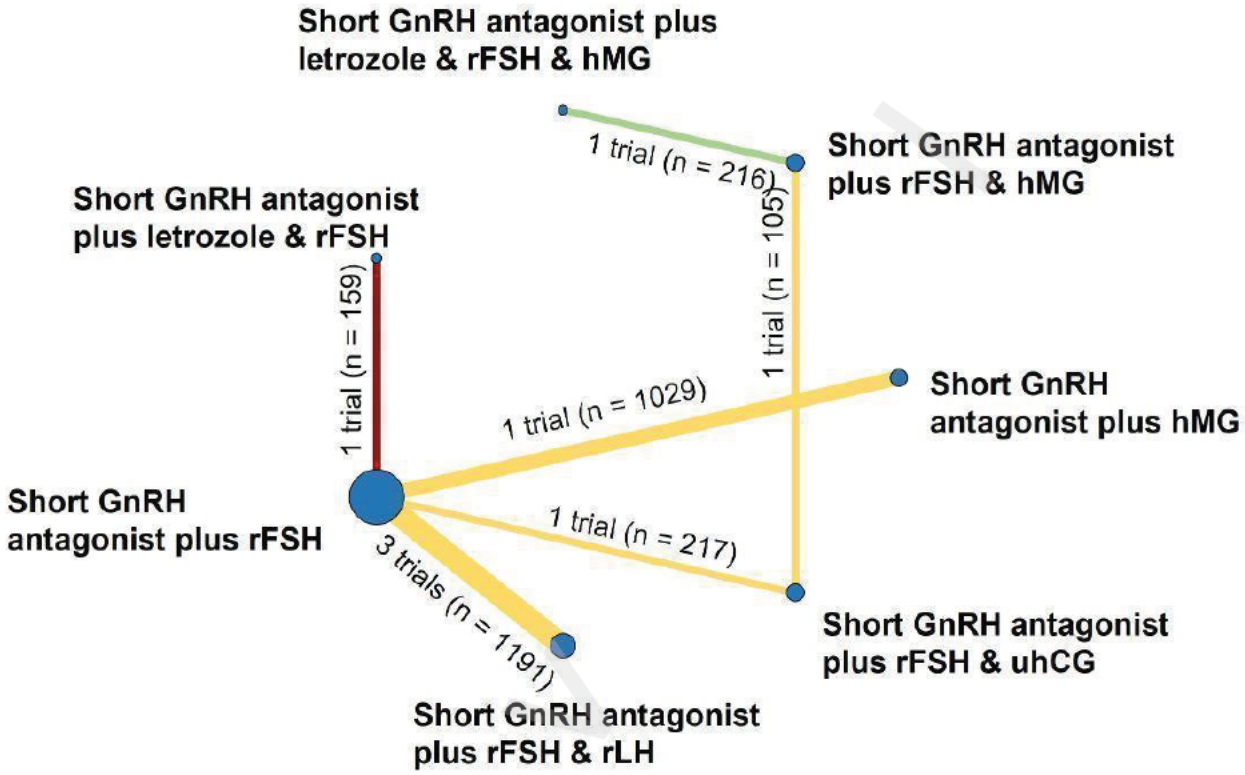
F r the seventeen remaining indirect comparisons, the network evid nce is either uncertain or very uncertain (for effect estimates, see Figure 78).

Short GnRH antagonist protocols

Figure 79 presents the network diagram for oocyte number in women with predicted normal response undergoing short GnRH antagonist protocols. The network was connected. There were six direct comparisons and fifteen indirect comparisons.

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Figure 79. Network diagram of short GnRH antagonist protocols for the outcome of oocyte number in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

hMG versus rFSH

Human menopausal gonadotrophin may r duce oocyte number versus rFSH (MD -2.16, 95% -3.59 to 0.74, 1 study, 1029 women; low-certainty evidence; Analysis 17.8)

rFSH & rLH versus rFSH

Combined rFSH and rLH may resu t in little to no difference in oocyte number ve sus rFSH (MD 0.68, 95% CI -1.42 to 0.06, 3 studies, 1191 women, I^2 = 19%; low-certainty evidence; Analysis 18.8).

rFSH & uhCG versus rFSH

Combined rFSH and uhCG may reduce the number of oocytes versus rFSH (MD -1.40, 95% CI -1.60 to -1.20, 1 study, 217 women; low-certainty evidence; Analysis 21.4).

rFSH & uhCG versus rFSH & hMG

Combined rFSH and uhCG may result in little to no difference in oocyte number versus combined rFSH and hMG (MD -0.40, 95% CI -3.21 to 2.41, 1 study, 105 women; low-certainty evidence; Analysis 23.4).

Letrozole & rFSH versus rFSH

The evidence is very uncertain about this comparison (MD 0.30, 95% CI -0.87 to 1.47, 1 study, 159 women; very low-certainty evidence; Analysis 26.4).

Letrozole, rFSH & hMG versus rFSH & hMG

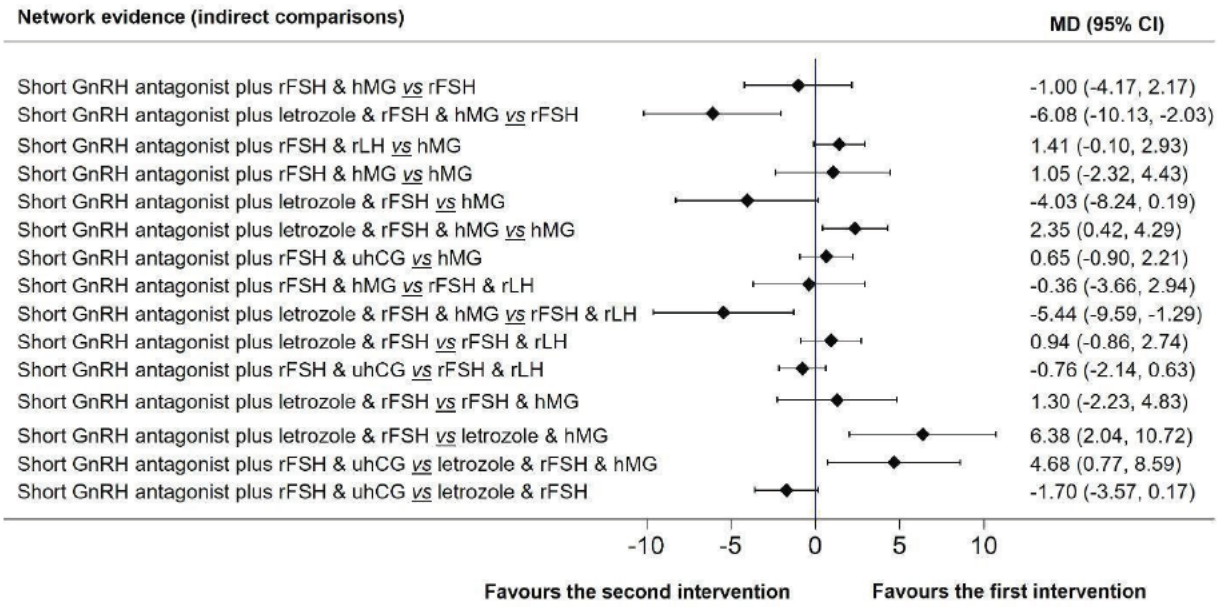
Combined letrozole, rFSH and hMG probably reduce oocyte number versus rFSH and hMG (MD -5.08, 95% CI -7.39 to -2.77, 1 study, 216 women; moderate-certainty evidence; Analysis 27.5).

Network estimates (indirect evidence)

For the fifteen remaining indirect comparisons, the network evidence is either uncertain or very uncertain (for effect estimates, see Figure 80).

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Figure 80. Forest plot comparing short GnRH antagonist protocols with mean difference (MD) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of oocyte number in women with predicted normal response.



Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of oocy e number in women with predicted normal response.

9.2. Women with predicted HIGH response

Pituitary suppression methods

There was only one direct comparison between pituitary suppression methods for the outcome of oocy e num er in women with predicted high response (short GnRH a tagonist versus long GnRH agonist).

Short GnRH antagonist versus long GnRH agonist

Short antagonist protocols may result in little to no difference to oocyte number versus long agonist protocols (MD -0.08, 95% CI 1.58 to 1.41, 3 studies, 434 women, I^2 = 0%; low-certainty evidence; Analysis 1.9).

Long GnRH agonist protocols

Figure 81 presents the network diagram for oocyte number in women with predicted high response undergoing long GnRH agonist protocols. The network was connected. There were two direct comparisons and one indirect comparison. The evidence is very uncertain for all direct (Analysis 6.9 and Analysis 1.9) and network (Figure 82) estimates.

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Figure 81. Network diagram of long GnRH agonist protocols for the outcome of oocyte number in women with predicted high response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is red for very low-certainty evidence.

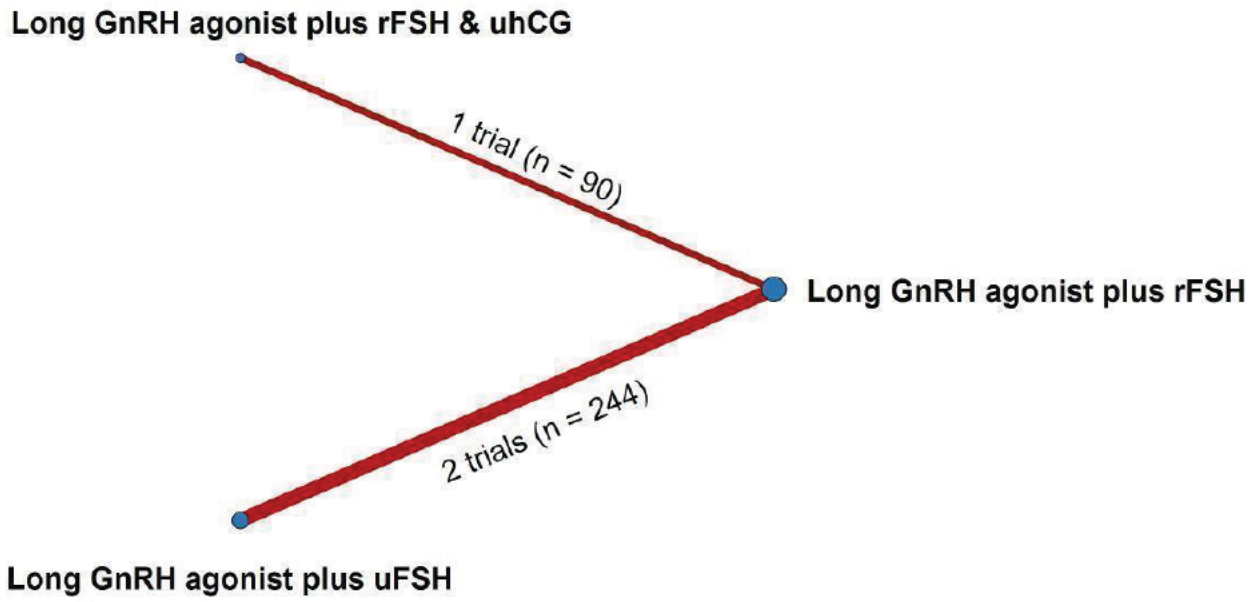
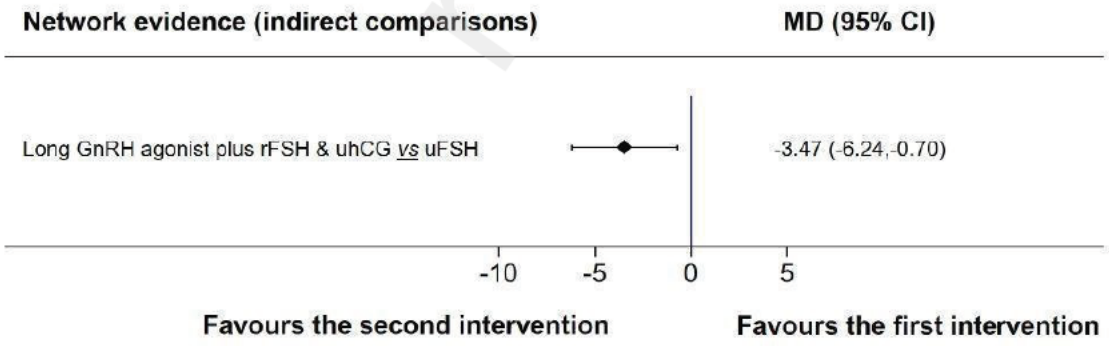


Figure 82. Forest plot comparing long GnRH agonist pr tocols with mean difference (MD) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of oocyte number in women with predicted high response.



Short GnRH antagoni t protocols

There was only one direct comparison for oocyte number in women with predicted high response undergoing short GnRH antagonist protocols (hMG versus rFSH).

hMG versus rFSH

Human menopausal gonadotrophin probably reduces oocyte number versus rFSH (MD -7.10, 95% CI -8.81 to -5.39, 1 study, 619 women; moderate-certainty evidence; Analysis 17.8).

Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of oocyte number in women with predicted high response.

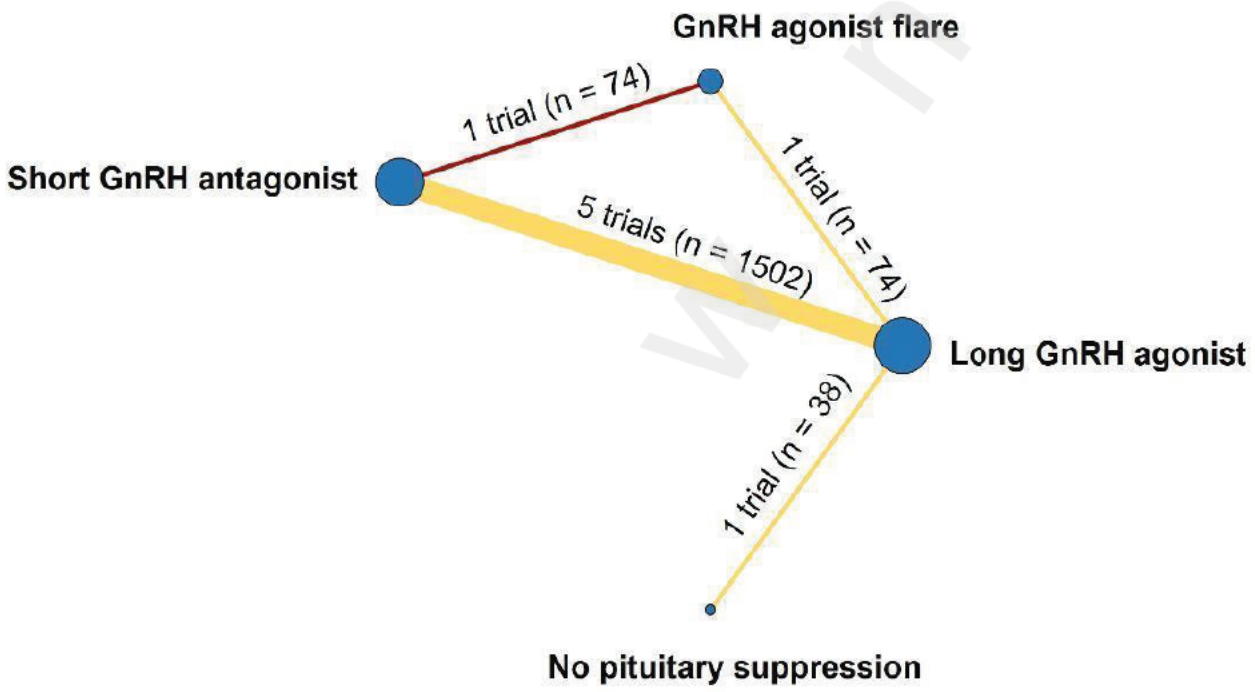
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9.3. Women with predicted LOW response

Pituitary suppression methods

Figure 83 shows the network diagram of pituitary suppression methods for the outcome of oocyte number in women with predicted low response. The network was connected. There was one comparison for which only direct evidence was available; three comparisons for which both direct and indirect evidence were available; and two indirect comparisons.

Figure 83. Network diagram of pituitary suppression methods for the outcome of oocyte number in women with predicted low response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of t ials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparison

No pituitary suppression versus long GnRH agonist

Ovarian stimulation without pitu tary suppression may result in little to no difference in oocyte number versus long GnRH agonist protocols (MD -0.50, 95% CI -1 01 to 0.01, 1 study, 38 women; low-certainty evidence; Analysis 3.6).

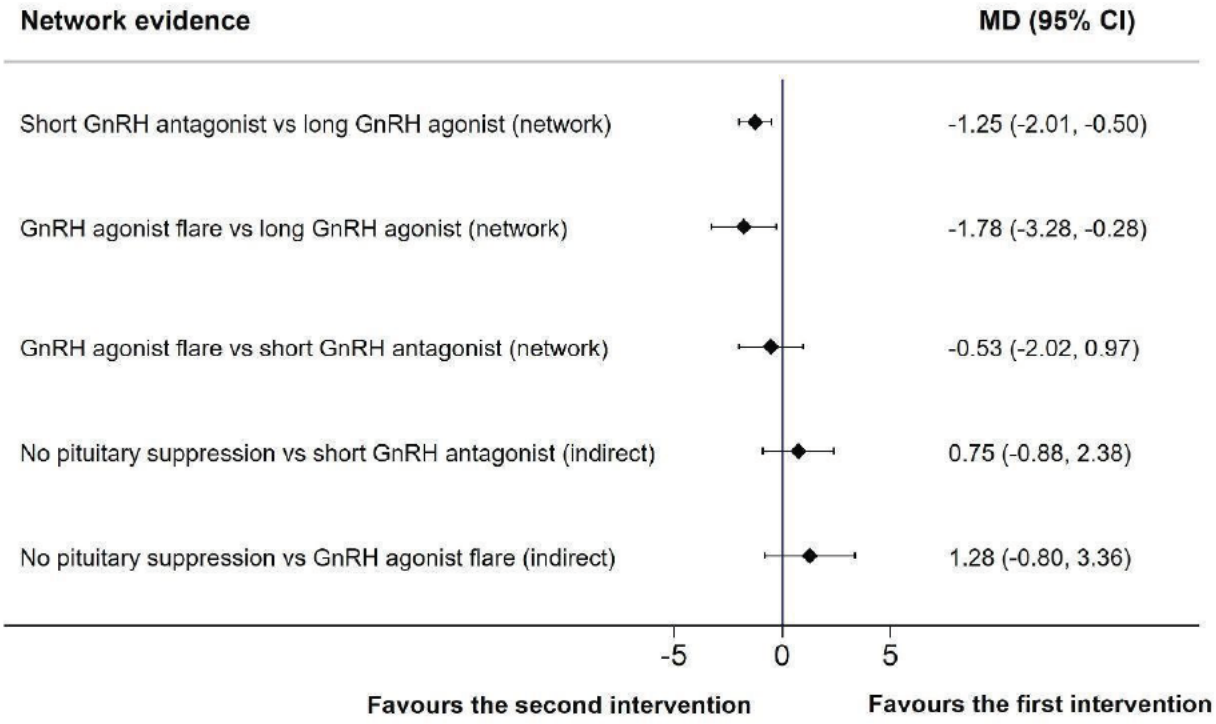
Network estimates

Short GnRH antagonist versus long GnRH agonist (direct and indirect evidence)

Short antagonist protocols may reduce oocyte number versus long agonist protocols (MD -1.25, 95% CI -2.01 to -0.50; low-certainty evidence; direct estimates: Analysis 1.9; network estimates: Figure 84).

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Figure 84. Forest plot comparing pituitary suppression methods with mean difference (MD) and 95% confidence intervals (CI) from network meta-analysis (network estimates combining direct and indirect evidence; where no RCTs were conducted for a specific comparison, only the indirect estimate is presented) for the outcome of oocyte number in women with predicted low response.



GnRH agonist flare versus long GnRH agonist (direct and indirect evidence)

GnRH agonist flare protocols may reduce oocyte number versus long GnRH agonist protocols (MD -1.78, 95% CI -3.28 to -0.28; low-certainty evidence; direct estimates: Analysis 2.6; network estimates: Figure 84).

GnRH agonist flare versus short GnRH antagonist (direct and indirect evidence)

The network evidence is very uncertain about this comparison (MD -0.53, 95% CI -2.02 to 0.97; very low-certainty evidence; direct estimates: Analysis 4.3; network estimates: Figure 84).

No pituitary suppression versus short GnRH antagonist (indirect evidence only)

Ovarian stimulation without pituitary suppression may result in little to no difference in oocyte number versus short GnRH antagonist protocols (MD 0.75, 95% CI -0.88 to 2.38; low-certainty evidence; Figure 84).

No pituitary suppression versus GnRH agonist flare (indirect evidence only)

The network evidence for this comparison is very uncertain (MD 1.28, 95% CI -0.80 to 3.36; very low-certainty evidence; Figure 84).

Long GnRH agonist protocols

There was only one direct comparison for oocyte number in women with predicted low response undergoing long GnRH agonist protocols (rFSH & rLH versus rFSH).

rFSH & rLH versus rFSH

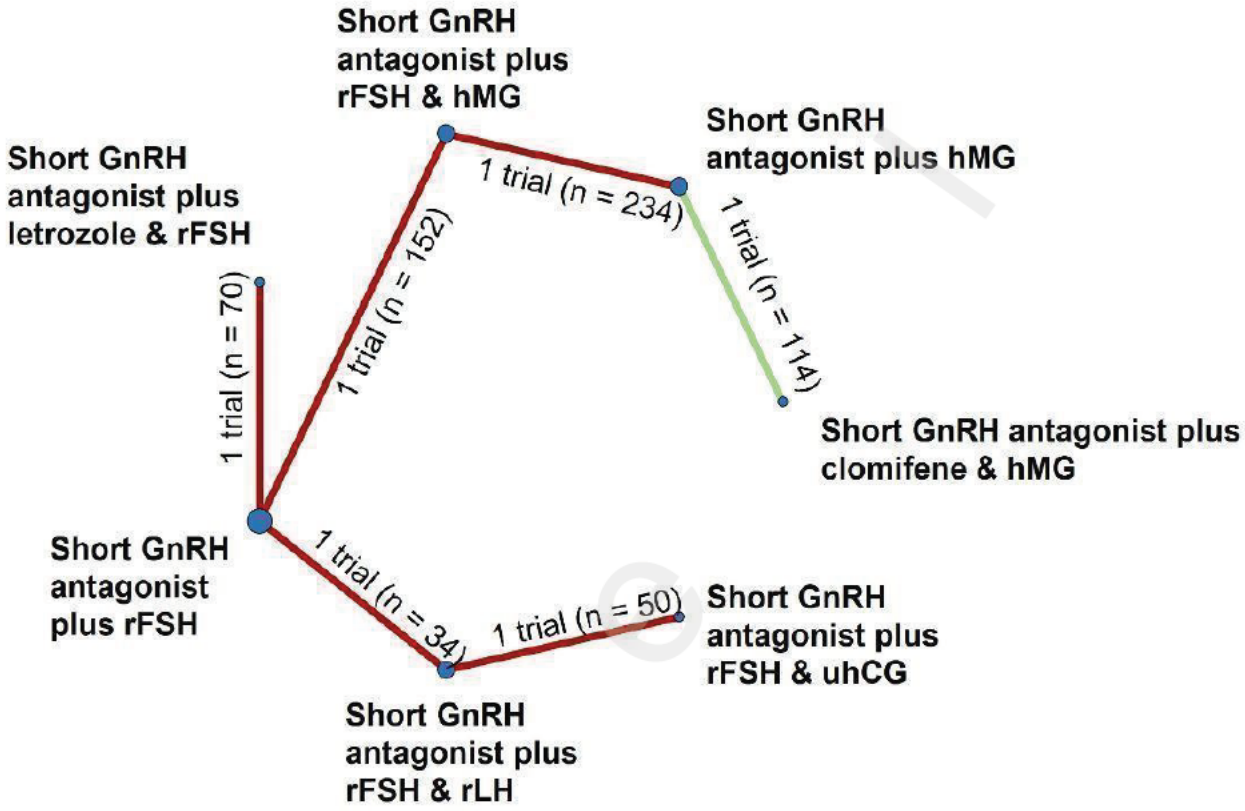
The evidence is very uncertain about this comparison (MD 1.24, 95% CI -1.89 to 4.38, 2 studies, 1069 women, I2 = 96%; very low-certainty evidence; Analysis 10.9).

Short GnRH antagonist protocols

Figure 85 presents the network diagram for oocyte number in women with predicted low response undergoing short GnRH antagonist protocols. The network was connected. There were six direct comparisons and fifteen indirect comparisons.

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Figure 85. Network diagram of short GnRH antagonist protocols for the outcome of oocyte number in women with predicted low response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence and red for very low-certainty evidence.



Direct comparisons

rFSH & rLH versus rFSH

The evidence is very uncertain about th comparison (MD -1.30, 95% CI -2.90 to 0.30, 1 study, 34 women; very low-certainty evidence; Analysis 18.8).

rFSH & hMG versus rFSH

The evidence is very unc rtain a out this comparison (MD 0, 95% CI -0.92 to 0.9 , 1 s dy, 15 women; very low-certainty evidence; Analysis 9.5).

rFSH & hMG versus hMG

The evidence is very uncertain about this comparison (MD -0.70, 95% CI -1.46 to 0.06, 1 study, 234 women; very low-certainty evidence; Analysis 20.8).

rFSH & uhCG versus rFSH & rLH

The evidence is very uncertain about this comparison (MD 1.50, 95% CI -0.64 to 3.64, 1 study, 50 women; very low-certainty evidence; Analysis 22.5).

Clomifene & hMG versus hMG

Combined clomifene and hMG probably increase oocyte number versus hMG (MD 0.32, 95% CI 0.05 to 0.59, 1 study, 114 women; moderate-certainty evidence; Analysis 24.3).

Letrozole & rFSH versus rFSH

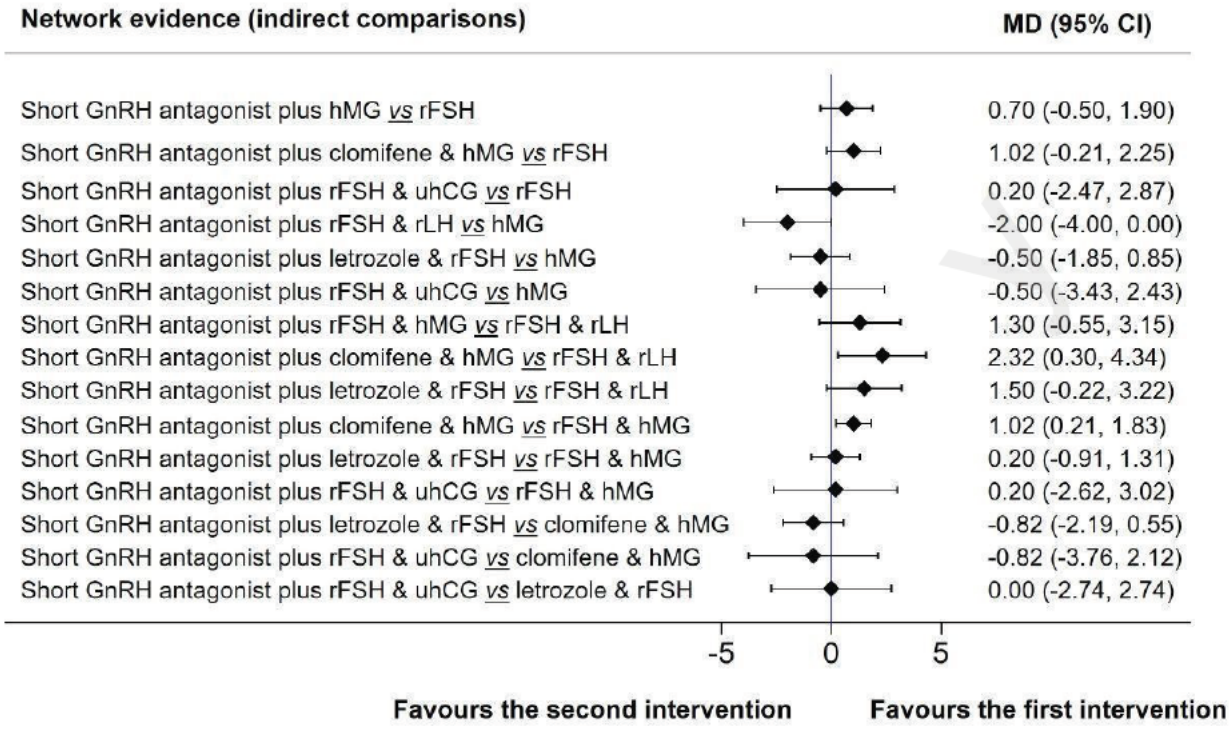
The evidence is very uncertain about this comparison (MD 0.20, 95% CI -0.42 to 0.82, 1 study, 70 women; very low-certainty evidence; Analysis 26.4).

Network evidence (indirect evidence only)

For the remaining fifteen indirect comparisons, the network evidence is very uncertain of the effect of each intervention versus its comparator (very low-certainty evidence; for effect estimates, see Figure 86).

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Figure 86. Forest plot comparing short GnRH antagonist protocols with mean difference (MD) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of oocyte number in women with predicted low response.



GnRH agonist flare protocols

There was only one direct comparison for oocyte number in women with predicted low response undergoing GnRH ag nist flare protocols (rFSH & rLH versus rFSH).

rFSH & rLH versus rFSH

Combined rFSH and rLH probably reduce oocy e number versus rFSH (MD -0.23, 95% CI -0.43 to -0.03, 1 study, 84 wo en; moderate-certainty evidence; Analysis 28.2).

Progestogens

The quantitative analysis did not include any studies comparing protocols using progestogens or pituitary suppression and different gonadotrophin types for e outcome of oocyte number in women with predicted low response.

No pituitary suppression

There was only one direct comparison for oocyte number in women with predicted w re ponse undergoing ovarian stimulation without pituitary supp ession (rFSH & hMG versus uFSH & hMG).

rFSH & hMG versus uFSH & hMG

Combined rFSH and hMG may increase oocyte number versus combined uFSH and hMG (MD 1.60, 95% CI 0.17 to 3.03, 1 study, 30 women; low-certainty women; Analysis 29.2).

10. Number of cleavage-stage embryos

10.1. Women with predicted NORMAL response

Pituitary suppression methods

The quantitative analysis did not include any studies comparing different pituitary suppression methods for the outcome of number of cleavage-stage embryos in women with predicted normal response.

Long GnRH agonist protocols

Figure 87 presents the network diagram for the number of cleavage-stage embryos in women with predicted normal response undergoing long GnRH agonist protocols. The network was connected. There were two direct comparisons and one indirect comparison. The evidence is very uncertain for all direct (Analysis 6.10 and Analysis 14.9) and indirect (Figure 88) estimates.

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Figure 87. Network diagram of long GnRH agonist protocols for the outcome of cleavage embryo number in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is red for very low-certainty evidence.

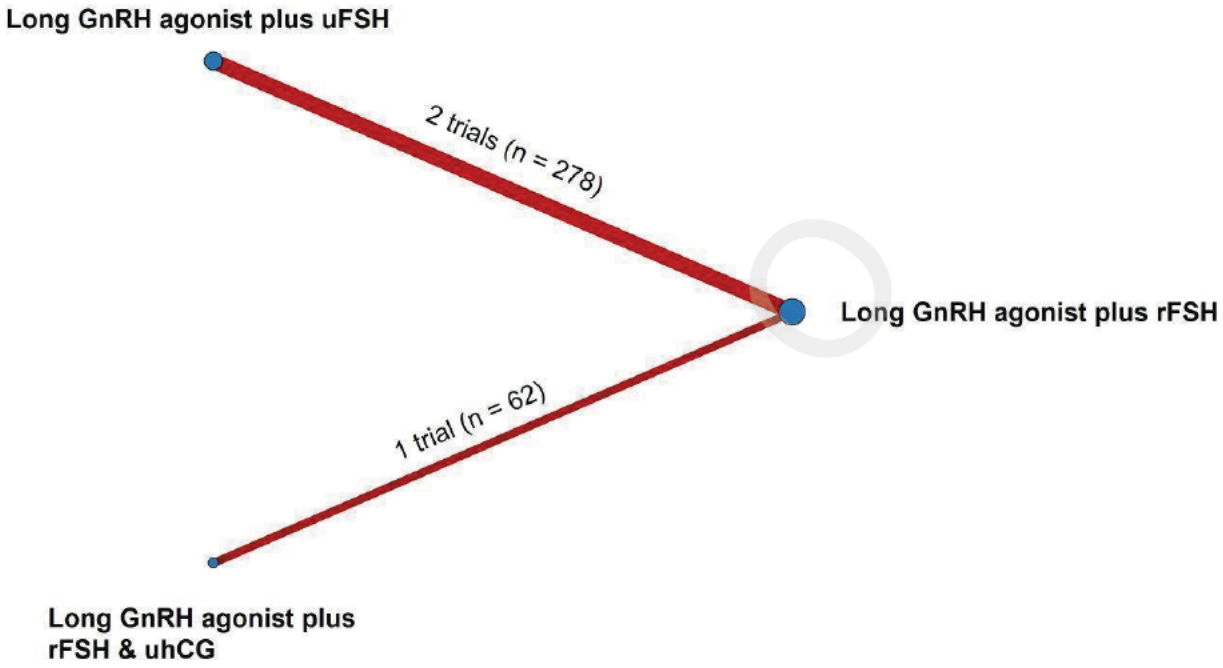
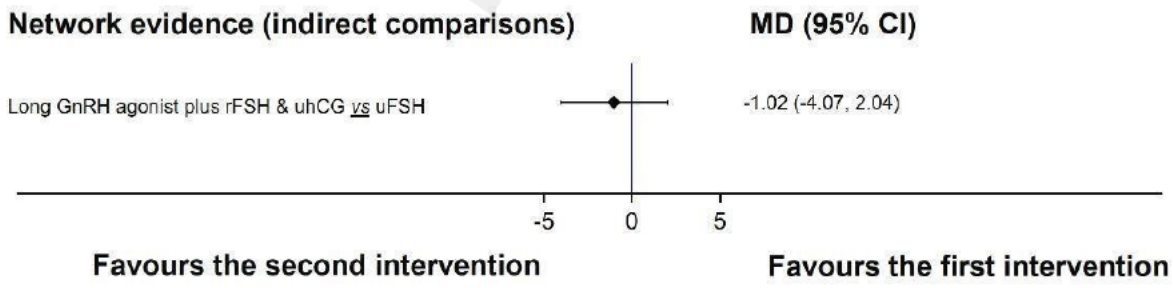


Figure 88. Forest plot comparing long GnRH agonis protocols with mean difference (MD) and 95% confidence intervals (CI) from network meta-analysi (in rect comparisons only) for the outcome of cleavage embryo number in women with predicted normal respon



Short GnRH antagoni t protocols

There was only one direct comparison for the number of cleavage-stage embryos in women with predicted normal response undergoing short GnRH antagonist protocols (hMG versus rFSH).

hMG versus rFSH

Human menopausal gonadotrophin probably reduces the number of cleavage-stage embryos versus rFSH (MD -0.80, 95% CI -1.28 to -0.32, 1 study, 749 women; moderate-certainty evidence; Analysis 17.9).

Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the outcome of the number

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of cleavage-stage embryos in women with predicted normal response.

10.2. Women with predicted HIGH response

Pituitary suppression methods

The quantitative analysis did not include any studies investigating the number of cleavage-stage embryos in women with predicted high response.

10.3. Women with predicted LOW response

In this subgroup of women, the included studies investigated only one direct comparison for the number of cleavage-stage embryos (short GnRH antagonist plus rFSH & hMG versus hMG).

Short GnRH antagonist plus rFSH & hMG versus hMG

In women with predicted low response undergoing short GnRH antagonist protocols, combined rFSH and hMG may reduce the number of cleavage-stage embryos versus hMG (MD -0.50, 95% CI -0.89 to -0.11, 1 study, 234 women; moderate-certainty evidence; Analysis 20.9).

11. Number of blastocysts

11.1. Women with predicted NORMAL response

Pituitary suppression methods

There were two direct comparisons between pituitary suppress on methods for the outcome of blastocyst number in women with predicted normal response (no pituitary suppression versus l ng GnRH agonist; and progestogens versus short GnRH antag nis) The network was disconnected. Network meta-analy is was not possible.

Direct comparisons

No pituitary suppression versus long GnRH ag nist

Ovarian stimulation without pitu ary suppression probably reduces the number of blastocysts ver us long GnRH agonist protocols (MD -3.30, 95% CI -3.85 to -2.75, study, 564 women; moderate-certainty evidence; Anal sis 3.7).

Progestogen versus short GnRH antagonist

The evidence is very uncer ain abo t this comparison (MD -0.20, 95% CI -0.74 to 0.34, 1 st dy, 31 women; very low-certainty evidence; Analysis .3).

Long GnRH agonist p tocols

The quantitative analysis did not include any studies comparing long GnRH agonist protocols using different gonadotrophin types for the outcome of blastocyst number in women with predicted normal response.

Short GnRH antagonist protocols

There was only one direct comparison for blastocyst number in women with predicted normal response undergoing short GnRH antagonist protocols (short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH).

hMG versus rFSH

Human menopausal gonadotrophin probably reduces slightly or has no effect on the number of blastocysts versus rFSH (MD -0.40, 95% CI -0.80 to 0, 1 study, 748 women; moderate-certainty evidence; Analysis 17.10).

Other networks - GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did no incl de any studies comparing interventions within these etworks fo the outcome of blastocyst number in women with predicted normal response.

11.2. Women with p edicted HIGH response

There was nly on dire t comparison investigating blastocyst number in women with predicted high response (short GnRH antagonis plus hMG versus short GnRH antagonist plus rFSH).

Short GnRH ant g ist plus hMG versus rFSH

In women with predicted high response undergoing short GnRH antagonis protocols, hMG probably reduces the number of blas ocys s ersus rFSH (MD -2.90, 95% CI -3.69 to -2.11, 1 study, 619 omen moderate-certainty evidence; Analysis 17.10).

11.3 Women with predicted LOW response

Onl one direct comparison investigated blastocyst number in women with predicted low response (short GnRH antagonist plus clomifene & hMG versus short GnRH antagonist plus hMG).

Short GnRH antagonist plus clomifene & hMG versus hMG

In women with predicted low response undergoing short GnRH antagonist protocols, combined clomifene and hMG probably result in little to no difference in the number of blastocysts versus hMG (MD 0.04, 95% CI -0.10 to 0.18, 1 study, 114 women; moderate-certainty evidence; Analysis 24.4).

12. Number of cryopreserved embryos

12.1. Women with predicted NORMAL response

Pituitary suppression methods

There was only one comparison between pituitary suppression methods for the number of cryopreserved embryos in women with predicted normal response (short GnRH antagonist versus long GnRH agonist).

Short GnRH antagonist versus long GnRH agonist

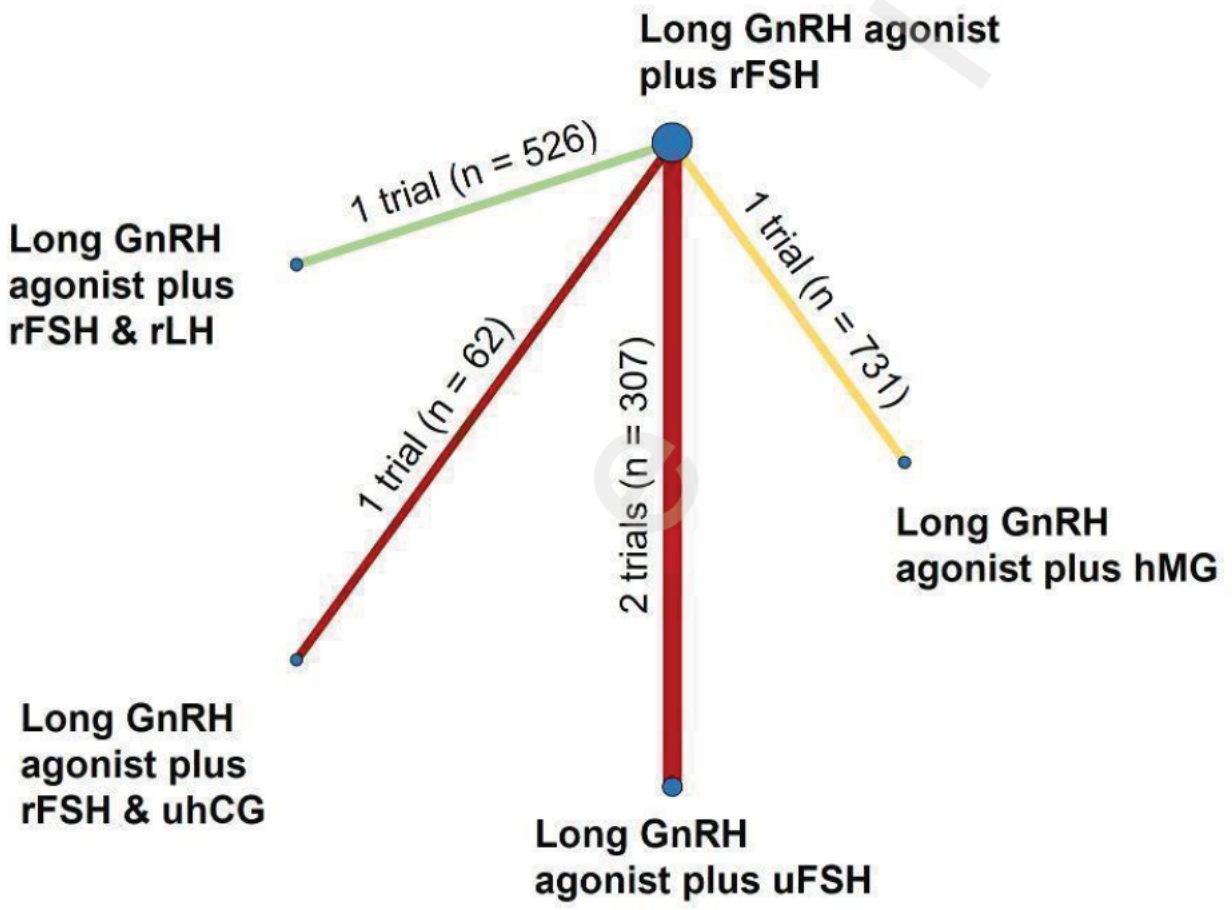
In women with predicted normal response, short antagonist protocols may result in little to no difference in the number of cryopreserved embryos versus long agonist protocols (MD -0.16, 95% CI -0.33 to 0.01, 5 studies, 2032 women, $I^2 = 34\%$; low-certainty evidence; Analysis 1.10).

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Long GnRH agonist protocols

Figure 89 presents the network diagram for the number of cryopreserved embryos in women with predicted normal response undergoing long GnRH agonist protocols. The network was connected. There were four direct comparisons and six indirect comparisons.

Figure 89. Network diagram of long GnRH agonist protocols for the outcome of frozen embryo number in women with predicted normal response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is green for moderate-certainty evidence; amber for low-certainty evidence; and red for very low-certainty evidence.



Direct comparisons

uFSH versus rFSH

The evidence is very uncertain about this comparison (MD -0.35, 95% CI -1.92 to 1.22, 2 studies, women, I^2 = 62%; very low-certainty evidence; Analysis 6.11)

hMG versus rFSH

Human menopausal gonadotrophin may result in little to no difference in the number of cryopreserved embryos versus rFSH (MD -0.10, 95% CI -0.51 to 0.31, 1 study, 731 women; low-certainty evidence; Analysis 7.9).

rFSH & rLH versus rFSH

Combined rFSH and rLH probably result in little to no difference in the number of cryopreserved embryos versus rFSH (MD -0.10, 95% CI -0.48 to 0.28, 1 study, 526 women; moderate-certainty evidence; Analysis 10.10).

rFSH & uhCG versus rFSH

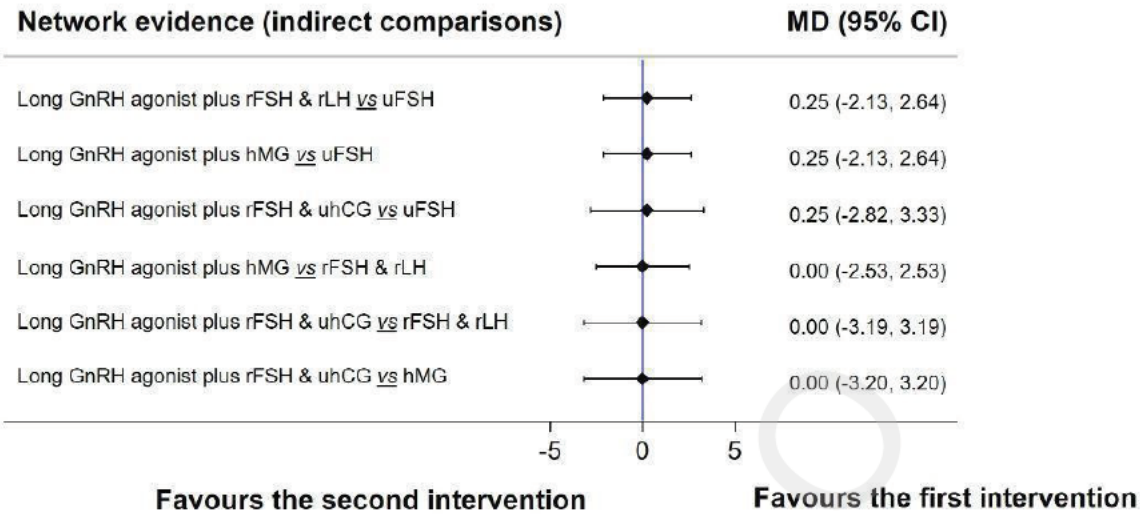
The evidence is very uncertain about this comparison (MD -0.10, 95% CI -2.09 to 1.89, 1 study, 62 women; very low-certainty evidence; Analysis 14.10).

Network estimates (indirect evidence only)

For the six remaining indirect comparisons, the network evidence is either uncertain or very uncertain (for effect estimates, see Figure 90).

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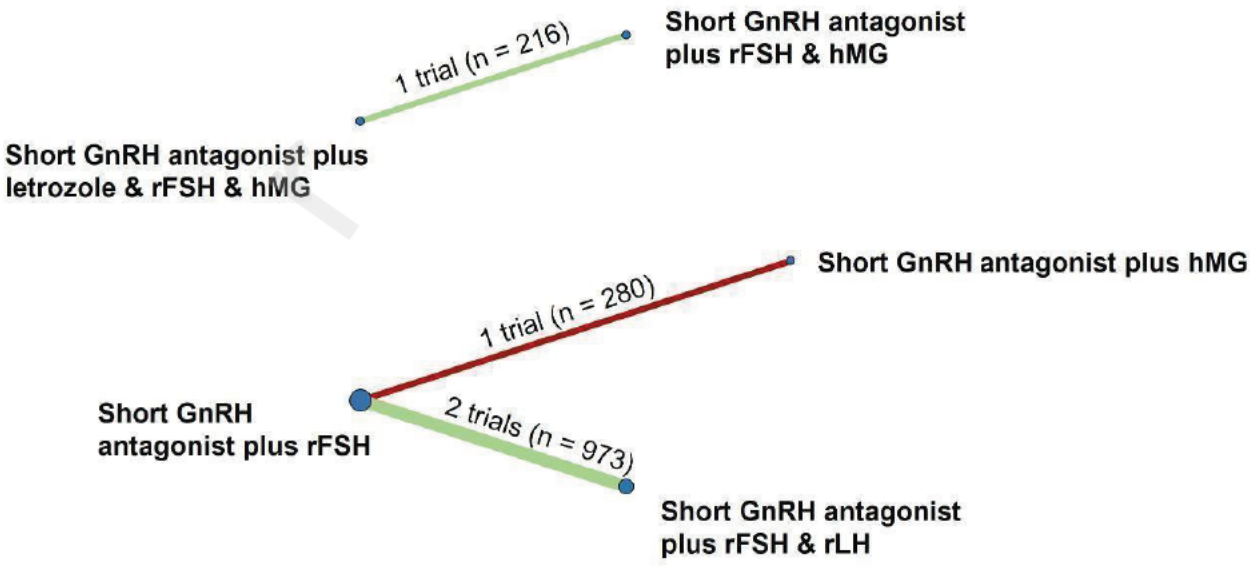
Figure 90. Forest plot comparing long GnRH agonist protocols with mean difference (MD) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of frozen embryo number in women with predicted normal response.



Short GnRH antagonist protocols

Figure 91 presents the network diagram for the number of cryopreserved embryos in women with predicted normal response undergoing short GnRH antagonist protocols. The network was disconnec d. There were three direct comparisons and one i direc comparison.

Figure 91. Network diagram of short GnRH antagonist protoco for the outcome of frozen embryo number in women with predicted normal response. The nodes repres nt an intervention and their size is proportional to the number of trials comparing this intervention to any ther in the network. The lines connecting each pair of interventions represent a direct comparison (random sed controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comp ris n. The numbers on the lines represent the number of trials and in brackets the number of participants ev l ated within each comparison. The colour of the line is green for moderate-certainty evidence and red for ve y low-certainty evidence.



Direct comparisons

hMG versus rFSH

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The evidence is very uncertain about this comparison (MD -0.10, 95% CI -0.57 to 0.37, 1 study, 280 women; very low-certainty evidence; Analysis 17.11).

rFSH & rLH versus rFSH

Combined rFSH and rLH probably reduce the number of cryopreserved embryos versus rFSH (MD -0.35, 95% CI -0.62 to -0.07, 2 studies, 973 women, I2 = 0%; moderate-certainty evidence; Analysis 18.9).

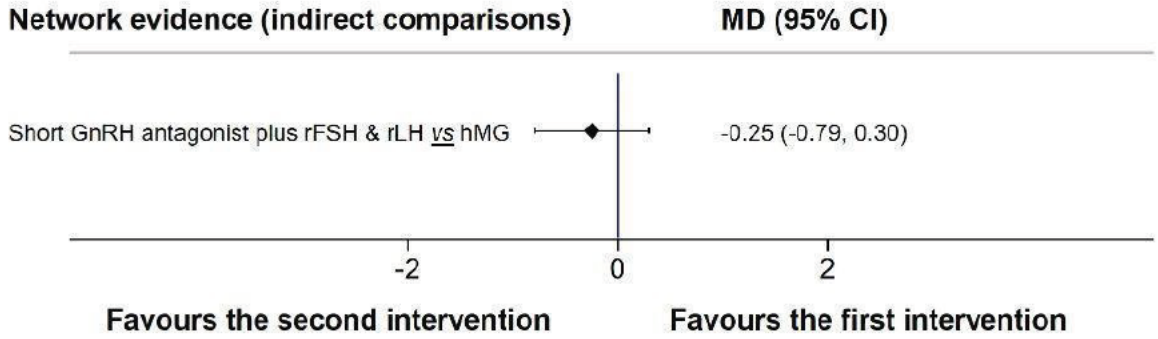
Letrozole, rFSH & hMG versus rFSH & hMG

Combined letrozole, hMG and rFSH probably reduce the number of cryopreserved embryos versus hMG and rFSH (MD -3.09, 95% CI -4.69 to -1.49, 1 study, 216 women; moderate-certainty evidence; Analysis 27.6).

Network estimates (indirect evidence only)

For the remaining indirect comparisons, the network evidence is very uncertain (for effect estimates, see Figure 92).

Figure 92. Forest plot comparing short GnRH antagonist protocols with mean difference MD) and 95% confidence intervals (CI) from network meta-analysis (indirect estimates only) for the outcome f froz n embryo number in women with predicted normal response.



Other networks - GnRH agonist flare protocols; progestogens fo pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the nu ber of cryopreserved embryos in women with predicted normal response.

12.2 Women with predicted HIGH response

Pi uitary suppression methods

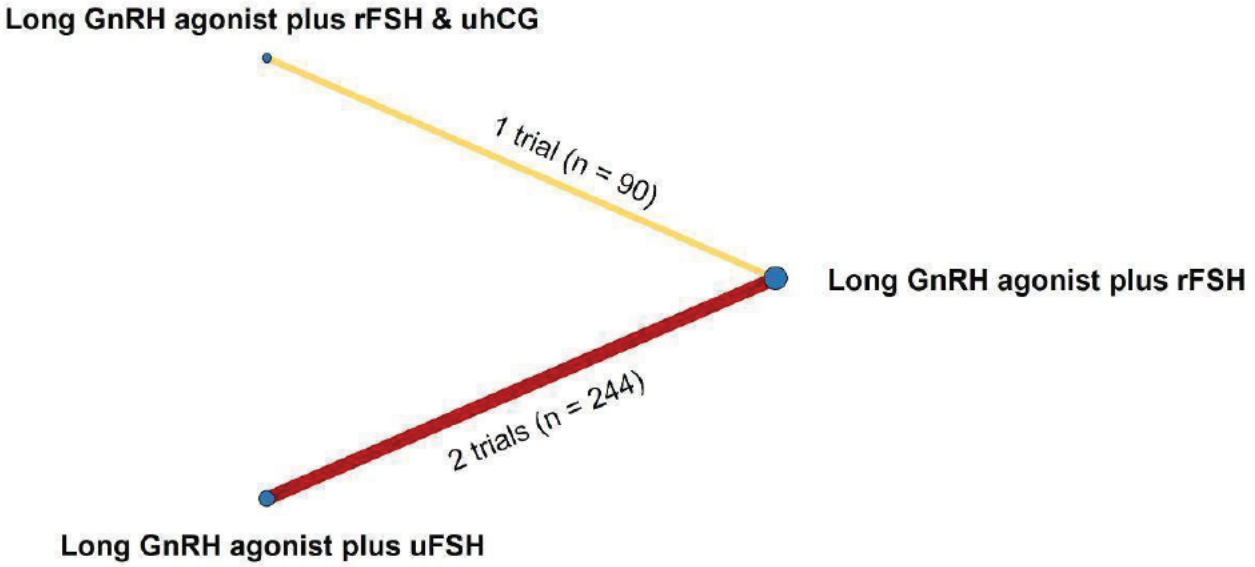
The quantitative analysis did not include any studies comparing pituitary suppression methods for the outcome of number of cryopreserved embryos in women with predicted high response.

Long GnRH agonist protocols

Figure 93 shows the network diagram for the number of cryopreserved embryos in women with predicted high response undergoing long GnRH agonist protocols. The network was connected. There were two direct comparisons and one indirect comparison.

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Figure 93. Network diagram of long GnRH agonist protocols for the outcome of frozen embryo number in women with predicted high response. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison (randomised controlled trial evidence) and their width is proportional to the number of trials evaluating each direct comparison. The numbers on the lines represent the number of trials and in brackets the number of participants evaluated within each comparison. The colour of the line is amber for low-certainty evidence and red for very low-certainty evidence.



Direct comparisons

uFSH versus rFSH

The evidence is very uncertain about this comparison (MD 0.94 95% -1.11 to 3.00, 2 studies, 244 women, I^2 = 66%; very low certainty evidence; Analysis 6.11).

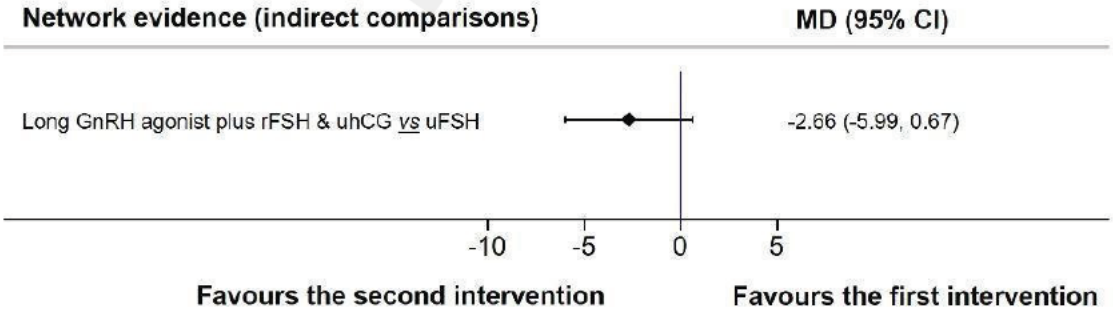
rFSH & uhCG versus rFSH

Combined rFSH and uhCG may reduce the number of cryopreserved embryos versus rFSH (MD -1.72, 95% CI -2.11 to -1.32, 1 study, 90 women; low-certainty evidence; Analysis 14.10).

Network estimates (indirect evidence only)

For the remaining indirect comparison (rFSH & uhCG versus uFSH), the network evidence is very uncertain (for effect estimates, see Figure 94).

Figure 94. Forest plot comparing long GnRH agonist protocols with mean difference (MD) and 95% confidence intervals (CI) from network meta-analysis (indirect comparisons only) for the outcome of frozen embryo number in women with predicted high response.



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Other networks - short GnRH antagonist protocols; GnRH agonist flare protocols; progestogens for pituitary suppression; and ovarian stimulation without pituitary suppression

The primary analysis did not include any studies comparing interventions within these networks for the number of cryopreserved embryos in women with predicted high response.

12.3. Women with predicted LOW response

Pituitary suppression methods

There was only one direct comparison between pituitary suppression methods for the number of cryopreserved embryos in women with predicted low response (short GnRH antagonist versus long GnRH agonist).

Short GnRH antagonist versus long GnRH agonist

Short antagonist protocols may result in little to no difference in the number of cryopreserved embryos versus long GnRH agonist protocols (MD -0.34, 95% CI -0.79 to 0.11, 1 study, 66 women; low-certainty evidence; Analysis 1.10).

Long GnRH agonist protocols

The quantitative analysis did not include any studies comparing long GnRH agonist protocols using different gonadotrophin types for the number of cryopreserved embryos in women with predicted low response.

Short GnRH antagonist protocols

There was only one direct comparison between short GnRH antagonist protocols for the number of cryopreserved embryos in women with predicted low response.

rFSH & hMG versus rFSH

The evidence is very uncertain about this comparison (MD 0.30, 95% CI -0.04 to 0.64, 1 study, 152 women; very low ce tainty evidence; Analysis 19.6).

Other networks - GnRH agonist flare prot cols; progestogens for pituitary suppression; and ovarian stimulati n with ut pituitary suppression

The primary analysis did not include ny studies comparing interventions within these networks fo the number of cryopreserved embryos in women with predicted low response.

DISCUSSION

Summary of main resul s

This review included 326 RCTs investigating a total of 56 different COS protocols in 541 articipants whose response was predicted as normal or unsta d in 221 trials (68%), high in 28 trials (8%), and low in 77 tria s (24%). Below we provide a summary of network comparisons for which we found moderate-certainty evidence investigating the primary outcomes (live birth and OHSS) according to predicted response. We also present network comparisons for which there was moderate-certainty of a difference between interventions investigating the secondary outcomes. For the remaining network comparisons and outcomes, the evidence did not confidently identify a difference between interventions.

Primary outcomes – network comparisons (primary analysis)

In women with predicted normal response, when comparing different pituitary suppression methods, the use of short antagonist protocols probably results in little to no difference in live birth, and a reduction in OHSS, when compared with long agonist protocols. For the remaining participant subgroups (low- and high-responding women), the evidence was either of low or very low-certainty.

In women with predicted high response, when comparing different short antagonist protocols using different gonadotrophins for the primary outcomes, we found moderate-certainty evidence that hMG reduces the risk of OHSS vers s rFSH. The evidence was of low or very low certainty or the rema ning participant subgroups (normal- and low-responding omen).

Secondary outcomes

Multiple pregnancy

In women with predicted normal response undergoing long agonist protocols, we found moderate-certainty evidence that combined rFSH and hMG p bably increase multiple pregnancy versus rFSH.

Miscarr age

In wom n with predicted normal response undergoing short antagonist protocols, combined letrozole, hMG and rFSH probably reduce iscarriage rate versus hMG and rFSH.

n women with predicted low response undergoing long agonist pro ocols, combined rFSH and rLH probably reduce miscarriage versus rFSH.

Cancellation

In women with predicted high response having short antagonist protocols, there was moderate-certainty evidence that hMG increases the risk of cancellation versus rFSH.

Oocyte number

In women with predicted normal response, agonist flare protocols probably reduce oocyte number versus long agonist protocols. When comparing all long agonist protocols, combined rFSH and rLH probably reduce oocyte number versus rFSH alone. When comparing all short antagonist protocols, the evidence showed that combined letrozole, rFSH and hMG probably reduce oocyte number versus combined rFSH and hMG.

In women with predicted high response undergoing short antagonist protocols, hMG probably reduces oocyte number versus rFSH.

In women with predicted low response having short antagonist protocols, combined clomifene and hMG probably increase oocyte number versus hMG. Further, agonist flare protocols with combined rFSH and rLH probably reduce oocyte number versus rFSH in this subgroup of women.

Number of cleavage-stage embryos

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In women with predicted normal response undergoing short antagonist protocols, hMG probably reduces the number of cleavage-stage embryos versus rFSH.

Blastocyst number

In women with predicted normal response, ovarian stimulation without pituitary suppression probably reduces the number of blastocysts versus long agonist protocols. When comparing different short antagonist protocols, hMG probably reduces slightly or has no effect on the number of blastocysts versus rFSH.

In women with predicted high response undergoing short protocols, hMG probably reduces the number of blastocysts versus rFSH.

Number of cryopreserved embryos

When comparing different short antagonist protocols in women with predicted normal response, combined rFSH and rLH probably reduce the number of cryopreserved embryos versus rFSH; and combined letrozole, hMG and rFSH probably reduce the number of cryopreserved embryos versus combined hMG and rFSH.

Overall completeness and applicability of evidence

This review investigated existing direct and indirect evidence on the relative effectiveness and safety of COS protocols. Our findings are therefore applicable to the overall population presenting for IVF. We were not able to confidently establish rankings of the different interventions due to challenges with grouping treatments under single networks, the existence of many disconnected networks the large number of interventions, the lack of closed loops within networks and the low number of trials and events per interventio node. However, this is the first systematic review investig ting both direct and indirect comparisons between existing ovar an stimulation regimens according to women's predicted response o COS. In addition, using established methodology f om ochrane and GRADE, we conducted a comprehensive asses ment o study quality and evidence certainty for direct and network stimates.

Our results support a recent shift in pract e from administering long agonist protocols to using short antagon st protocols instead, in the interest of patient safety by re ucing OHSS rates, in women with predicted normal and high respons We found evidence that this practice probably does not affect the prim ry efficacy outcome of live birth in these two subgroups of women.

Importantly, out of 326 included studies, only 171 were suitable for meta-analysis due to limitati ns pertaining to study quality or the way in which trialists repo ed thei results (e.g., per cycle rather than per woman randomised). Most of our correspondence with study authors remained unanswered at the time of publication, at least in part due many studies dating back one to two decades. For older studies, in ddition to contacting the authors directly, we conducted a thorough review of risk of bias assessments of all published Cochrane reviews on the subject of COS since 2010, and adjusted our own assessment of risk of bias and study quality according to how previous review authors documented their correspondence with trialists at the time.

Quality of the evidence

We restricted our primary analyses to studies judged to be at low risk of selection and other biases, in line with recent Cochrane practice. Although this ensured that our findings were based solely on trials whose risk of bias was overall low, it also diminished the pool of studies included in the meta-analysis, possibly reducing the statistical power and confidence of our primary results. Nonetheless, our sensitivity analyses including all studies, irrespective of risk of bias, largely agreed with our primary findings. In some cases, the sensitivity analyses provided additional information about the effect size and certainty of the evidence. For example, the s nsitivity analyses identified a probable reduction in OHSS tes wi short antagonist versus long agonist protocols in wom n with predicted high response, which had not been confidently iden fied in t e primary analyses.

Additional sensitivity analyses ccounting for effect modifiers other than predicted response (age, BMI, ethnicity) either were not possible ow ng to a l ck of s udies, or yielded similar conclusions to the prima analyses. his was also the case for sensitivity analyses using OR r ther than RR to report effect estimates.

Overall, our confidence in the evidence as assessed by the GRADE framework ranged from very low to moderate certainty. The main reasons or downgrading included substantial risk of bias as judged by ROB-1 tool, imprecision due to low event numbers and wide confidence intervals, and inconsistency due to inter-study hete og neity.

ot ntial biases in the review process

Five review authors have been involved in four of the included trials. SKS, AC and YK were investigators in Sunkara 2014. NSM was an investigator in Hohmann 2003; and FJB was an investigator in Hompes 2008. These review authors were not involved in the study selection process, data extraction or judgements about study quality and evidence certainty.

The included studies were conducted from 1987 to 2022. During this 34-year period, trial methodology has evolved, and ART procedures have improved substantially. There have been advances in the manufacturing process and purification of gonadotrophin preparations, and other changes, such as the introduction of GnRH antagonist and progestogen cycles, intracytoplasmic sperm injection, extended embryo culture to the blastocyst stage, time-lapse technology and embryo cryopreservation. While some of these interventions may have acted as effect modifiers for individual comparisons, it is plausible to expect that the distribution of such modifiers did not vary substantially, thus supporting the assumption of transitivity for the network analyses.

We elected to amalgamate patients whose predicted response was unstated by trialists with those with predicted normal response. This followed from a careful review of inclusion criteria in such studies, to ensure that they represented the general IVF population presenting for COS.

Finally, we elected to restrict our primary analyses to studies at low risk of selection and other biases after the original protocol had been published, but before the data had been extracted. This decision was based on recent concerns with data validity and veracity across a number of trials in reproductive medicine, and followed Cochrane Editorial guidance.

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Agreements and disagreements with other studies or reviews

Various reviews have investigated COS protocols in recent years, although very few have reported results according to predicted response to ovarian stimulation.

In a Cochrane review of different GnRH agonist protocols (Siristatidis 2015), the authors found moderate-quality evidence of higher clinical pregnancy in long agonist versus agonist flare protocols. Although our review did not confidently identify a difference in clinical pregnancy, ongoing pregnancy and live birth between the two protocols, our findings suggest that long agonist protocols improve the oocyte number in women with predicted normal and low response. We also found in this subgroup of women, agonist flare protocols with combined rFSH and rLH probably reduce oocyte number versus rFSH.

Our findings agree with those of Al-Inany 2016, who compared different antagonist protocols to agonist protocols. The authors did not confidently identify a difference in live birth, but found that short antagonist protocols resulted in fewer cases of OHSS compared to long agonist regimens.

The most recent Cochrane review investigating urinary versus recombinant gonadotrophins was conducted over a decade ago (Van Wely 2011). The authors included 42 trials investigating 9,644 women. The results suggested a slight reduction in live birth using rFSH versus hMG. Importantly, all downregulation methods were amalgamated in the meta-analyses, and the results were not reported according to predicted response. Further, methodolog involved in evidence grading has since evolved substantially. In our review, we did not confidently identify a difference betwe n gonadotrophin preparations across all pituitary downregu tion methods and predicted patient response to stimulation.

A previous Cochrane review compared protocols using FSH alone versus combined rFSH and rLH for ovarian stimul tion (M chtar 2007). The authors found that rFSH and rLH prob bly improved ongoing pregnancy rates, although there were insuffi ent data to make confident inferences about live birth. In addition, the investigators did not confidently find a diffe ence in miscarriage rates. Our results differ from those of ochtar 2007 in that we found that ovarian stimulation with combined SH and rLH probably results in little to no difference in ongoing pregnancy versus rFSH in long agonist protocols for normal-responding women. Further, in women with predicted low response undergoing long agonist protocols, we found that combined rFSH and rLH probably reduce miscarriage rate versus rFSH O r find ngs also suggest that the combination of rFSH and LH appe rs to reduce oocyte number versus rFSH alone in long agonist rotocols, and the number of cryopreserved embryos in short antagonist protocols.

The results of our re ew agree with those of Kamath 2017, who did not confidently iden fy a difference in effectiveness and safety between protocols using oral medications in combination with gonadotrophins versus gonadotrophins only for COS.

Finally, Lambalk 2017 conducted a systematic review and meta-analysis comparing short GnRH antagonist versus long agonist protocols accounting for predicted patient response. The primary outcome was the ongoing pregnancy rate. The authors included 50 RTCs investigating 9,950 women. A total of 34 trials focused on the general IVF population, 10 trials focused on women with PCOS, and 6 studies included only women with predicted low response. The evidence identified a slight reduction in ongoing pregnancy with short GnRH antagonist protocols in the general population, but no confident difference in high- and low-responding women. Importantly, the authors did not confidently find a difference in live birth between the two types of protocols, although this may have been due to the inclusion of fewer studies investigating this outcome in comparison to ongoing pregnancy. Our findings differ from those of Lambalk 2017 in that we report moderate-certainty evidence indicating that short GnRH antagonist protocols probably result in little to no difference in ongoing pregnancy or live birth in women with predicted normal resp nse.

AUTHORS' CONCLUSIONS

Implications for pr ctic

The findings of this sy tematic review and NMA support the use of short GnRH an gonis protocols versus long GnRH agonist protocols n women ith predicted normal and high response undergoin COS. Our esults confidently demonstrate that short antagonist protocols probably result in lower rates of OHSS without affecting the live birth rate per participant. However, we were unable to confidently identify differences in gonadotrophin preparat ons in protocols using similar methods for pituitary sup r ssion The evidence for such comparisons was judged to be of low or very low certainty, limiting the clinical applicability of ou f dings. In addition, we were unable to create a ranking o all interventions according to effectiveness and safety owing to the igh number of networks and interventions but low number of par icipants and events per intervention. We present a thorough synthesis of direct and indirect evidence between various COS according to patient response, however, which should inform clinicians when making management decisions.

Implications for research

Nearly half of included trials in this review were not suitable for the primary analysis due to substantial methodological flaws. While we were still able to identify moderate-certainty evidence for some outcomes, the design limitations in many of the studies resulted in comparisons featuring low and very low certainty. There is a need for high-quality trials investigating different COS protocols that remain understudied in some subgroups of women (e.g., comparing different gonadotrophin preparations in women with predicted high and normal response). Future randomised trials should focus on strengthening the certainty of the existing evidence, in addition to further exploring positive signals identified by this review. For example, it would be important to further investigate the effect of adding LH activity (either by administering hMG or rLH) to FSH protocols on oocyte, blastocyst and frozen embryo numbers in women with different predicted response profiles. The number of frozen embryos resulting from a particular stimulation cycle is particularly important to ascertain the long-term effectiveness of COS protocols. In addition, future trials should endeavour to report cumulative treatment rates (e.g., cumulative ongoing pregnancy and live birth rates) accounting for all embryo transfers (fresh and frozen) following a single stimulation cycle.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS) or the Department of Health and Social Care.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abate 2009

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** multicentre **Recruitment period:** March 2007 to October 2008 **Sample size (total):** 401
Participants	**Inclusion criteria:** age 26–38 years; BMI 19–30 kg/m^2; basal SH <10 IU/l; estradiol <80 pg/ml; 10 antral follicles 2–10 mm in size; fewer than three prior oocyte retrievals; uterine cavity consistent with normal expected function as assessed through hysterosalpingogram, sonohysterography or hysteroscopy within 12 months from the beginning of the study, normal haematology and blood chemistry values; normal thyroid stimulating hormone level or euth roid (TSH could be low if secondary to exogenous thyroid medication as long as the patient wa euthyroid by normal free thyroxine level). Each patient was permitted to cycle once under the study p tocol. **Exclusion criteria:** POI; one or bo h ovarie inaccessible for oocyte retrieval; previous ovarian hyperstimulation syndrome; PCOS; stage I I or stage IV endometriosis; persistent ovarian cysts >20 mm; untreated hydrosalpinx; oocyte donation; any contraindication to pregnancy; abnormal bleeding of undetermined origin; uncontroll d thyr id or adrenal dysfunction; neoplasia; severe impairment of renal or hepatic function; and use of medications that might interfere with study evaluations (e.g. hormonal medication, prostaglandin inhib ors, psychotropic agents). **Predicted response as stat d by the trialists:** unstated **Oocyte donors:** no **Cause o infe tility:** various **Subgr up (ge):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**A m 1:** long agonist plus uFSH (n = 215) **Arm 2:** long agonist plus rFSH (n = 186) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** various **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** ongoing pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript

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Abate 2009 *(Continued)*

Trial registration: unstated

Registration date: -

Conflict of interest declaration: none declared

Funding: unstated

Author correspondence: yes - antonino.abate@gmail.com (15 September 2021)

Calculations used to obtain absolute event numbers: yes

Inclusion in meta-analysis: no (unclear allocation concealment; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomisatio "
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, although o ly objective outcomes included in the meta-analyses.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, al hough only objective outcomes included in the meta-analyses.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT ot performed and not possible to extract data from stated percentages for the majority of outcomes. Loss to follow-up unstated.
Selective reporting (reporting bias)	Low ri k	Trial conducted and published pre-2010. No evidence of selective reporting.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Abdelmassih 2006

Study characteristics

Methods

Design: randomised controlled trial

Country: Brazil

Language: English

Setting: single centre

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Abdelmassih 2006 *(Continued)*

	Recruitment period: unstated
	Sample size (total randomised): 206
Participants	**Inclusion criteria:** age <35 years
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): yes (<35 years)
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 103)
	Arm 2: long agonist plus rFSH (n = 103)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: vaginal progest rone
Outcomes	**Outcomes reported:** ongoing pregnan y; miscarriage
	Outcomes included in the meta-an lysis: none
Notes	**Type of publication:** conferen e abstract
	Trial registration: unstated
	Registration date:
	Conflict of interest declaration: unstated
	Funding: uns ated
	Author cor espondence: none undertaken
	Calculations used to obtain absolute event numbers: yes
	In lusion in meta-analysis: no (unclear risk of selection bias; primary review outcomes not reported)
	A ditional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.

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Abdelmassih 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Loss to follow-up unstated.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010 Sele tive re orting not detected.
Other bias	Low risk	Trial conducted pre-2010 S ngle entre tudy with plausible recruitment rates. No concerns regarding v lidity of re ults. Effect size difference lower than two-fold between trial arms.

Abd Rabbo 2012

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Egypt **Language:** English **Setting:** single centre **Recruitment perio :** un tated **Sample size (to al randomised):** 60
Participants	**Inclusi n cri ria:** ag <35 years; basal serum FSH <10 IU; minimal to mild endometriosis as diagnosed by laparoscopy and lesions classified according to the revised American Society for Reproductive Medicine scoring **Exclusion crit ria:** moderate or severe endometriosis according to the revised American Society for Reproductive Medicine scoring; potentially low-responding women; previous ovarian surgery **Pred ted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** yes (<35 years) **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG & uFSH (n = 30) **Arm 2:** long agonist plus letrozole (n = 30) **Fertilisation method:** ICSI

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Abd Rabbo 2012 *(Continued)*

	Embryo age at the time of transfer: cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number; number of cleavage-stage embryos **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - abdrabbo_100@yaho m, hassanclinic2000@yahoo.com (15 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support or j dgement
Random sequence generation (selection bias)	Unclear risk	Uns ated
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	nstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	H h risk	ITT analysis not performed but possible to extract for number of oocytes. Two women dropped out in the long agonist group, and three in the letrozole group. Loss to follow-up 10% in the letrozole group.
Selective reporting (reporting bias)	Low risk	Registration and study timeline not found. Selective reporting not detected.
Other bias	Unclear risk	Registration and study timeline not found. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Aboulghar 2010

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Egypt **Language:** English **Setting:** single centre **Recruitment period:** August 2008 to April 2009 **Sample size (total randomised):** 84
Participants	**Inclusion criteria:** age <39 years; PCOS (Rotterdam criteria); good physical he lth; normal basal FSH and prolactin levels **Exclusion criteria:** fibroids; endometriosis; general or medical disorders; BMI >35 kg/m^2; participation in previous IVF trials **Predicted response as stated by the trialists:** p edicted hig response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus uFSH (n 42) **Arm 2:** long agonist plus rFSH (n = 42) **Fertilisation method** IVF or ICSI **Embryo age at the me of t ansfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outc mes reported:** clinical pregnancy; ongoing pregnancy; multiple pregnancy; oocyte number; number f mbryos cryopreserved **Outcomes included in the meta-analysis:** clinical pregnancy; ongoing pregnancy; multiple pregnancy oocyte number; number of embryos cryopreserved
Notes	**Type o publication:** published full-text manuscript **Tria registration:** ISRCTN36808716 **Registration date:** 21 July 2009 **Conflict of interest declaration:** none declared **Funding:** "This study was sponsored in part by IBSA Institut Biochimique SA." **Author correspondence:** yes - ghar@link.net (15 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases)

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Aboulghar 2010 *(Continued)*

Additional comments: -

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed by picking one envelope for each patient from sequentially numbered envelopes".
Allocation concealment (selection bias)	Low risk	"Dark, sealed envelopes containing the intervention were created by a third party not involved in the allocation process".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded, subjective outcomes (cancellation) reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded, subjective ou comes (cancellation) reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Attrition per arm <10%.
Selective reporting (reporting bias)	Low risk	Selective reporti g not detected.
Other bias	Low risk	Trial cond ted p e-2010. Single centre study with plausible recruitment rates. No conc rns regarding validity of results. Effect size difference lower than two-fold etwee trial arms. No other biases detected.

Acevedo 2004

Study characteristics	
Methods	**Design:** rand mised controlled trial **Country:** Spain **La guage:** English **Setti g:** single centre **Rec itment period:** unstated **mple size (total randomised):** 42
Participants	**Inclusion criteria:** age >18 and ≤35 years; healthy; normal menstrual cycle **Exclusion criteria:** PCOS; endometriosis; hydrosalpinges; severe male factor **Predicted response as stated by the trialists:** unstated **Oocyte donors:** yes **Cause of infertility:** various **Subgroup (age):** no

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Acevedo 2004 *(Continued)*

	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 20)
	Arm 2: short antagonist plus rFSH & rLH (n = 22)
	Fertilisation method: N/A
	Embryo age at the time of transfer: N/A
	Luteal phase support: N/A
Outcomes	**Outcomes reported:** ongoing pregnancy; oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscrip
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - ehernand m@fivmadrid.es (15 September 2021)
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: no (high risk of other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	**Authors' judgemen**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list.
Allocation concealment (selection bias)	Unclear isk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.

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Acevedo 2004 *(Continued)*

Other bias	High risk	Trial conducted pre-2010. Single centre study with unclear timeline. No concerns regarding validity of results. Effect size difference higher than two-fold between trial arms for (e.g., implantation rate). No other biases detected.

Acharya 1992a

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United Kingdom **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 87
Participants	**Inclusion criteria:** unstated **Exclusion criteria:** unstated **Predicted response as stated by the t alists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicit):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 43) **Arm 2:** agonis flare plus hMG (n = 44) **Fertili atio method:** unstated **Embryo age the time of transfer:** unstated **Lu eal phase support:** hCG
Outcomes	**O tcomes reported:** oocyte number **Out omes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not found)

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Acharya 1992a *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated (…) using a predetermined schedule".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis perform No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Selective eporting not detected.
Other bias	Unclear risk	Single centre study. Recruitment timeline unstated. Study conducted pre 2010.

Adonakis 1998

Study characteristics

Methods	**De ign:** randomised controlled trial **Coun ry:** United Kingdom **Language:** English **tting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 40
Participants	**Inclusion criteria:** age <37 years; tubal or unexplained infertility; normal menstrual cycles; normal early follicular phase serum FSH concentrations **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated

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Adonakis 1998 *(Continued)*

	Oocyte donors: no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long GnRH agonist plus uFSH alone (n = 16) **Arm 2:** long GnRH agonist plus uFSH with uLH (hMG) for the final 2 days before hCG, after follicular phase stimulation with purified uFSH (n = 11) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	Pharmacokinetic outcomes analysed, none clinic l.
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** un t ted **Funding:** unstated **Author correspondence:** no e undertaken **Calculations used to obtain ab olute event numbers:** no **Inclusion in meta-analys s:** no (outcomes interest not reported therefore not included in the meta-analysis; no contact details f r the authors) **Additional comments:**

Risk of bias

Bias	Authors j dgement	Support for judgement
Random sequence generation (selection bias)	Un lear risk	"randomised to two groups", methodology unclear.
Allocation concealment (selection bias)	Unc ear risk	Unstated.
Blinding of part ipant and personnel (per - mance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias)	High risk	ITT analysis not strictly performed. Attrition >10% in both trial arms.

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Adonakis 1998 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	Single centre study with unclear recruitment timeline. Conducted pre-2010.

Aflatoonian 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** March 2009 to May 2011 **Sample size (total randomised):** 122
Participants	**Inclusion criteria:** age <38 years; regular m nstru l cycles (25–35 days); BMI <30 kg/m^2; normal uterus and ovaries on transvaginal ultrasound; b sal FSH <10 IU/l **Exclusion criteria:** severe endom trio s; PCOS; previous pelvic surgery; azoospermia; >2 previous IVF/ICSI cycle failures **Predicted response as stat d by he trialists:** unstated **Oocyte donors:** no **Cause of infertility:** vario s **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subg oup (ethnicity):** no
Interventions	**Arm 1:** long gonist plus hMG & uhCG (n = 60) **Arm 2:** long agonist plus hMG (n = 62) **Fertil sation method:** IVF or ICSI **Emb yo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** moderate to severe OHSS; clinical pregnancy; ongoing pregnancy; miscarriage **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** IRCT201107286420N5 **Registration date:** 1 September 2011

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Aflatoonian 2012 *(Continued)*

Conflict of interest declaration: none declared

Funding: "This project was funded by Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran."

Author correspondence: yes - eftekhar@ssu.ac.ir (15 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear allocation concealment; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computerised generated ist".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, howeve only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	IT anal sis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low sk	Trial conducted pre- and post-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms.

Aghahosseini 2014

Study characteri tics

Methods

Design: randomised controlled trial

Country: Iran

Language: English

Setting: single centre

Recruitment period: October 2012 to March 2012

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Aghahosseini 2014 *(Continued)*

	Sample size (total randomised): 137
Participants	**Inclusion criteria:** age 20-39 years; standard indications for ART; BMI 20-25 kg/m^2; normal uterus; two functional ovaries; day 3 FSH concentration <10 IU/l; estradiol concentration <60 pg/ml **Exclusion criteria:** low ovarian response in previous IVF/ICSI cycle; history of >2 previous unsuccessful IVF/ICSI attempts; any endocrine disorders **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH & uhCG (n = 72 **Arm 2:** short antagonist plus rFSH (n = 65) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** clea age stage (days 2-4) **Luteal phase support:** vaginal progestero e
Outcomes	**Outcomes reported:** OHSS; ongo ng p egnancy; oocyte number; number of cleavage-stage embryos **Outcomes included in the met analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** IRCT201211197165N2 **Registration date:** 25 November 2012 **Conflict of inte st declaration:** unstated **Fundi g:** uns ated **Author c r espondence:** yes - kashani_ladan@tums.ac.ir (15 September 2021) **Calculations used to obtain absolute event numbers:** yes **In usion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary utcomes [live birth and/or OHSS]) **Add ional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated code".
Allocation concealment (selection bias)	Unclear risk	Unstated.

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Aghahosseini 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers from percentages. Seven women dropped o t (five in the hCG group, and 2 in the non-hCG group). Attrition rate <10% both trial arms.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Trial conducted post-2010 nd p spec vely registered. Single centre study with plausible recruitme t rates. Eff ct size difference lower than two-fold between trial arms.

Akman 2000

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Turkey **Language:** English **Setting:** single centre **Recruitment perio :** un tated **Sample size (to al randomised):** 40
Participants	**Inclusi n cri ria:** two previous failed IVF attempts; FSH >15 mIU/l **Exclus n c iteria:** azoospermia **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **C use of infertility:** low ovarian reserve **Sub roup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** hMG & uFSH without pituitary suppression (n = 20) **Arm 2:** short antagonist plus hMG & uFSH (n = 20) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** unstated

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Akman 2000 *(Continued)*

	Luteal phase support: unstated
Outcomes	**Outcomes reported:** clinical pregnancy; ongoing pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - mbahceci@hotmail.com (15 eptember 2021) **Calculations used to obtain absolute event numbe** yes **Inclusion in meta-analysis:** no (unclear risk of se ection and other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgem nt
Random sequence generation (selection bias)	Unclear risk	"Consecu ive number method".
Allocation concealment (selection bias)	Unclear risk	Uns ated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclea risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed, and absolute event numbers extracted from percentages for more than one outcome (CPR, OPR). Four cycles cancelled in the hMG/uFSH-only group, and 5 in the short antagonist group. Attrition >10% in both trial arms.
Selective reportin (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates impossible to determine because study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Akman 2001

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Turkey **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 48
Participants	**Inclusion criteria:** low ovarian response as per clinical judgement, including at least two failed IVF attempts due to one of the following reasons: baseline FSH concentr tions >15 mIU/ml or oestradiol concentration on the day of hCG injection <500 pg/ml or numb of mature oocytes retrieved lower than four **Exclusion criteria:** azoospermia **Predicted response as stated by the trialists:** pre icted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus hMG & uFSH (n = 24) **Arm 2:** short antagonist plus hM & uFSH (n = 24) **Fertilisation meth d:** ICSI **Embryo age at the tim f transfer:** cleavage stage (days 2-4) **Luteal phase suppo t:** intramuscular progesterone
Outcomes	**Outcomes eported:** clinical pregnancy; ongoing pregnancy; cancellation; oocyte number **Outcomes inc uded in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Tri l registration:** unstated **Reg stration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - mbahceci@hotmail.com (15 September 2021) **Calculations used to obtain absolute event numbers:** yes **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported)

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Akman 2001 *(Continued)*

Additional comments: -

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective out omes rep rted.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed, absolute event numbers calculated from percentages for some outcomes (CPR, OPR). Five cycles were cancelled in group 1, and six in group 2. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Selective reporti g not detected.
Other bias	Unclear risk	Trial cond ted p e-2010. Single centre study, although recruitment rates unstated a it was not possible to ascertain the duration of the study.Effect size diffe ence lower than two-fold between trial arms. No other biases detected.

Albano 2000

Study characteristics	
Methods	**Design:** rand mised controlled trial **Country:** in ernational (Belgium, Germany) **La guage:** English **Setti g:** multicentre **Rec itment period:** unstated **mple size (total randomised):** 293
Participants	**Inclusion criteria:** age ≤39 years; regular menstrual cycles; FSH ≤10 IU/l; normal ovarian morphology; no more than three previous IVF/ICSI procedures **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various

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Albano 2000 *(Continued)*

	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus hMG (n = 198)
	Arm 2: long agonist plus hMG (n = 95)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: hCG or progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; multiple regna cy; miscarriage; ectopic pregnancy; cancellation; oocyte number; number of embryos cryopr served
	Outcomes included in the meta-analysis: live bi th; clinica pregnancy; multiple pregnancy; miscarriage; ectopic pregnancy; cancellation; oocyte number; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none under ken (author contact details not found)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)
	Additional comme ts:

Risk of bias

Bias	Autho s' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Centralised telephone procedure."
Allocation concealment (selection bias)	Low risk	"Centralised telephone procedure."
Blinding of particip nts and personnel (p rformance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Twenty women withdrew from the study after randomisation (10 in each

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Albano 2000 *(Continued)*

		group). Ten cycles were cancelled in the cetrorelix group, and eleven in the buserelin group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. No evidence of selective reporting.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Aletebi 2007

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Saudi Arabia **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 43
Participants	**Inclusion criteria:** baseline FSH levels 15 mIU/ml; the definition of poor response was an unsuccessful stimulation (no ovarian esponse when ≥300 IU of FSH were administered for ≥15 days) or low number of oocytes retrieved (<5) **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertil ty:** low ovarian reserve **Subgroup (age):** no **Subgro p (MI):** no **Subgroup (ethnicity):** no
Interventions	**Ar 1:** short antagonist plus rFSH (n = 23) **Arm 2:** agonist flare plus rFSH (n = 20) **Fertilisation method:** IVF **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated

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Aletebi 2007 *(Continued)*

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: yes - faletebi@yahoo.com (15 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, howeve o ly objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, h wever only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear isk	Trial conducted pre-2010. Single centre study. Recruitment timeline unstated, therefore rates impossible to determine. Effect size difference lower than two-fold between trial arms. No other biases detected.

Al-Jeborry 2019

Study characteristics

Methods

Design: randomised controlled trial

Country: Iraq

Language: English

Setting: multicentre

Recruitment period: June 2018 to September 2019

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Al-Jeborry 2019 *(Continued)*

	Sample size (total randomised): 158
Participants	**Inclusion criteria:** low-responding women **Exclusion criteria:** age >42 years; POI; severe endometriosis; endocrine disorder; thyroid diseases; azoospermia **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus rFSH (n = 41) **Arm 2:** short antagonist plus rFSH (n = 117) - two rms merge (see additional comments) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage tage (days 2-4) **Luteal phase support:** vaginal progesteron
Outcomes	**Outcomes reported:** clinical pregnancy cancellation; oocyte number **Outcomes included in the meta- na ysis** none
Notes	**Type of publication:** publish d full text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of inter st d claration:** unstated **Funding:** stated **Auth r correspondence:** yes - drmelal@yahoo.com (15 September 2021) **Calculations used to obtain absolute event numbers:** yes **In lusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes no reported) **Additional comments:** A total of 158 women with low response were randomly assigned to three groups: group 1 (n = 41) received a short agonist flare protocol with rFSH; group 2 (n = 77) received a sho t antagonist protocol; and group 3 (n = 46) underwent a "start-stop-start" antagonist protocol. For the purposes of meta-analysis, we planned to amalgamate groups 2 and 3.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated. Uneven distribution of participant numbers between trial arms.

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Al-Jeborry 2019 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but po sible to ex act absolute event numbers from percentages. A total of 9 cases were cancel ed in group 1 and a total of 15 in groups 2 and 3 (total = 24). A tritio >10%.
Selective reporting (reporting bias)	Unclear risk	Selective reporting not det cted
Other bias	Unclear risk	Trial conducted post-2010 Registra ion timeline unstated. Multicentre study. Effect size difference lower than two-fold between trial arms.

Al-Karaki 2011

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** unstated. **Language:** English **Setting:** unstated. **Recruitment pe iod:** unstated. **Sample size (otal r ndomised):** 124
Participants	**Inclusio c iteria:** low response (criteria unspecified) **Exclusion criteria:** unstated **P dicted response as stated by the trialists:** predicted low response **Oo yte donors:** no **Cau e of infertility:** low ovarian response **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus uFSH (n = 62) **Arm 2:** long agonist plus uFSH (n = 62) **Fertilisation method:** unstated

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Al-Karaki 2011 *(Continued)*

	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** conference abstract
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none undertaken (author c tact de ils not found)
	Calculations used to obtain absolute event nu bers: no
	Inclusion in meta-analysis: no (unclear risk of sele tion an other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support f r ju gement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Uns ated, subjective outcomes reported (e.g., cancellation).
Blinding of outcome assessment (detection bias) All outcomes	Unclear isk	Unstated, subjective outcomes reported (e.g., cancellation).
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Five cycles canceled in the short antagonist group, and four in the long agonist group. Attrition <10% in both trial arms.
Selective reporti g (reporting bias)	Unclear risk	Unclear.
Other bias	Unclear risk	Unclear.

Allegra 2011

Study characteristics

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Allegra 2011 *(Continued)*

Methods	**Design:** randomised controlled trial
	Country: Italy
	Language: English
	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 102
Participants	**Inclusion criteria:** age ≥38 years and/or basal FSH ≥9 mUI/ml
	Exclusion criteria: age ≥44 years; basal FSH ≥ 16 mUI/ml; severe en ometrios s; severe male factor; secondary infertility ≤3 years
	Predicted response as stated by the trialists: predicted low response
	Oocyte donors: no
	Cause of infertility: low ovarian reserve
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n 56)
	Arm 2: long agonist plus rFSH (n = 6)
	Fertilisation method: ICSI
	Embryo age at the time f tran fer: unstated
	Luteal phase suppo t: p ogesterone (route unstated)
Outcomes	**Outcomes repo ed:** view outcomes not reported
	Outcom s i cluded in the meta-analysis: none
Notes	**Type f pub ication:** conference abstract
	Trial registra ion: unstated
	Registration date: -
	Conflic of interest declaration: unstated
	Funding: unstated
	Author correspondence: none undertaken (author contact details not found)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

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Allegra 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., cancellation).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., ancel ation).
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed b t absolute event numbers reported. Four couples in group A and 1 n group B d d not start the treatment. Of those starting treatment, 5 cycles we e cancelled prior to oocyte retrieval in group A and 3 in group B. Additionally, embryo transferred was not performed in 5 women in group B. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Unclear risk	Unclear.
Other bias	Unclear risk	Unclear.

Alsbjerg 2017

Study characteristics	
Methods	**Design:** randomised c ntrol ed trial **Country:** Denmar **Lang age:** English **Setting:** s gle centre **Re ruitment period:** 2009 to 2011 **Sample size (total randomised):** 102
Participants	**Inclusion criteria:** age >18 years and ≤35 years; regular cycles (25–34 days); basal FSH and LH values on sec nd to third day of the cycle not exceeding 12 IU/l; BMI >18 and <30 kg/m^2; first or second IVF and intracytoplasmic sperm injection cycles; and absence of uterine abnormalities **Exclusion criteria:** medical diseases; PCOS; previous participation in the study **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2)

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Alsbjerg 2017 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & rhCG (n = 51) **Arm 2:** long agonist plus rFSH & rLH (n = 51) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; OHSS; clinical pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** live birth; OHSS; clinica pregnancy cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** EUdraCT: 2009-009375-35; NC 01339299 **Registration date:** 26 May 2009 **Conflict of interest declaration:** "PH received unrestricted study grants from Merck Serono, MSD, Ferring and IBSA as well as honoraria for lectures from Merck Serono, MSD and IBSA. CYA have conducted clinical research and lectures sponsored by Merck Serono, Ferring, MSD and IBSA." **Funding:** "This study was supported by an unrestricted research grant from Merck Serono, Denmark." **Author correspondence:** none underta en **Calculations used to obtain abso u e event numbers:** no **Inclusion in meta-analysis:** yes (pr mary analysis - low risk of selection and other biases) **Additional comments:**

Risk of bias

Bias	**Authors' judgement**	**upport for judgement**
Random sequence generation (selection bias)	Low risk	"Computer-generated random numbers".
Allocation concealment (selection bias)	Low risk	"Sealed, unlabelled envelopes, each containing a unique study number".
Blinding of participants and personnel (performance bias) All outcomes	High isk	Open label, subjective outcomes (OHSS) reported.
Blinding of outcome assessment (detection b s) All outcomes	High risk	Open label, subjective outcomes (OHSS) reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed, however possible to obtain absolute event data from the manuscript. Ten discontinued treatment in the rFSH plus hCG group, and 9 discontinued in the rFSH plus rLH group, therefore attrition >10% in both groups.

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Alsbjerg 2017 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial prospectively registered. All outcomes reported as stated in the registration.
Other bias	Low risk	Trial conducted pre- and post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Alvino 1995

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Australia **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 60
Participants	**Inclusion criteria:** age <39 years; BMI ≤26.7 kg/m^2; <4 previous assisted conception cycles; regular ovulatory cycles 21-35 days; infertility resulting fr m tubal problems; unexplained infertility >3 years; normal uterine cavity; presence of both ova ies; absence of hepatitis B; no recent ectopic pregnancy **Exclusion criteria:** stage III-IV endometriosis **Predicted response as stated by th trialists:** unstated **Oocyte donors:** no **Cause of infertility** various **Subgroup (age):** no **Subgroup (BMI):** y s (<30 kg/m^2) **Subg oup (e hnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 30) **Arm 2:** long agonist plus uFSH (n = 30) **rtilis tion method:** unstated **Emb yo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** moderate to severe OHSS; clinical pregnancy; number of embryos cryopreserved **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** -

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Alvino 1995 *(Continued)*

Conflict of interest declaration: unstated

Funding: "Supported by Serono (Australia)."

Author correspondence: none undertaken (author contact details not found)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however on y objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysi not strictly performed but possible to extract absolute event numbers. A total of nine women in each group (total = 18) did not reach egg collectio Att ition rate >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	el ctive reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Andersen 2006

Study characteristics

Methods

Design: randomised controlled trial

Country: International (Europe)

Language: English

Setting: multicentre

Recruitment period: February 2004 to December 2004

Sample size (total randomised): 731

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Andersen 2006 *(Continued)*

Participants	**Inclusion criteria:** age 21–37 years; regular menstrual cycles of 21–35 days and presumed to be ovulatory; tubal or unexplained infertility, including endometriosis stage I/II and mild male factor; eligible for IVF treatment; infertility for ≥1 year before randomisation, except for proven bilateral tubal infertility; BMI 18–29 kg/m^2; hysterosalpingography, hysteroscopy or transvaginal ultrasound documenting a uterus consistent with expected normal function (e.g., no clinically interfering uterine fibroids) within 3 years before randomisation; transvaginal ultrasound documenting the presence of both ovaries, without evidence of abnormality (e.g., no endometrioma) and normal adnexa (e.g., no hydrosalpinx) within 6 months before randomisation; early follicular phase serum FSH levels of 1–12 IU/l; willingness to accept transfer of one or two embryos; male partner with sperm quality compatible with fertilisation via IVF (results obtained within 12 months before randomisation) or previous clinical pregnancy; confirmation of downregulation before randomisation, defined as either menstrual bleeding and transvaginal ultrasound showing a shedded endometrium with a thickness of <5 mm and no ovarian cysts or serum oestradiol levels of <50 pg/ml (local laboratory) and transvaginal ultrasound howing no ovarian cysts **Exclusion criteria:** PCOS; endometriosis stage III-IV; severe male factor equiring ICSI; >2 previously consecutive unsuccessful IVF cycles; previous low response to IVF; previous unsuccessful fertilisation; previous severe OHSS; any significant systemic disease, e docrine or metabolic abnormalities; treatment with clomifene citrate, metformin, gonadotroph ns or GnRH analogues within 1 month before randomisation; pregnancy, lactation or cont aindication o pregnancy; current or past (3 months) smoking habit of >10 cigarettes per day; current or past (last 2 months) abuse of alcohol or drugs; history of chemotherapy (except for gestational condi ons) or adiotherapy; undiagnosed vaginal bleeding; tumours of the ovary, breast, adrenal gland, pituitary or hypothalamus and malformation of sexual organs incompatible with pregnancy; hypers nsitivity to any trial product **Predicted response as stated by the tria ts:** u stated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 363) **Arm 2:** long agonist plus rFSH (n = 368) **Fertilis tion method** IVF **Embry ag at the time of transfer:** cleavage stage (days 2-4) **Luteal phase upport:** vaginal progesterone
Outcomes	**O comes reported:** live birth; OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; cancellation; o cyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** live birth; OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; cancellation; oocyte number; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** "Anders Nyboe Andersen has conducted clinical research sponsored by Ferring Pharmaceuticals, Serono, Organon, Novo Nordisk and Medicult. Paul Devroey has conducted clinical research sponsored by Ferring Pharmaceuticals, Organon and Serono. Joan-Carles Arce is employee of Ferring Pharmaceuticals."

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Andersen 2006 *(Continued)*

Funding: "The study was sponsored by Ferring Pharmaceuticals A/S."

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Sealed sequentially numbered envelopes to conceal treatment allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial, subjecti outcome (OHSS) reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label trial, su jecti outcomes (OHSS) reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analys s perfo med. Nineteen cancellations in the hMG group and one drop out (to l = 20); twenty-one cancellations in the rFSH group and one drop out (total = 22). Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Select reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Antoine 1990a

Study characteristics

Methods	**Des n:** randomised controlled trial **untry:** France **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 180
Participants	**Inclusion criteria:** age <38 years; normo-ovulatory (with plasma progesterone >10 ng/ml in the luteal phase); complete or incomplete tubal obstruction; duration of infertility >3 years; no associated male factor

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Antoine 1990a *(Continued)*

	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 90)
	Arm 2: hMG without pituitary suppression (n = 90)
	Fertilisation method: unstated
	Embryo age at the time of transfer: cleavage stage (days 2-)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; ongoing pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number
	Outcomes included in the meta-analysis: one
Notes	**Type of publication:** published full ex manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration unstated
	Funding: unstated
	Author correspond nce: none undertaken (author contact details not found)
	Calculations use to obtain absolute event numbers: no
	Inclu on in meta-analysis: no (unclear risk of selection bias; primary review outcomes not reported)
	Additiona comments: -

Risk of bias

Bias	Autho s' judgement	Support for judgement
Random sequence enera tion (selection bias)	Unclear risk	Unstated.
Allocation concealm nt (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Unstated, subjective outcomes reported.

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Antoine 1990a *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Attrition rate <10% in both trial arms. Thirteen women were cancelled in the agonist group, and 26 in the hMG-only group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study. R cruitment rates unclear as study timeline unstated. Effect size difference low r than two-fold between trial arms. No other biases detected.

Ashkenazi 1989

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Israel **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomise):** 18
Participants	**Inclusion criteria:** PCOS **Exclusion criteria:** un ted **Predicted response as stated by the trialists:** predicted high response **Oocyte donors** o **Cause of infe tility:** PCOS **Subgrou age):** no **Subgroup (BMI):** no **Su group (ethnicity):** no
Interventions	**Arm 1:** uFSH without pituitary suppression (n = 6) **Arm 2:** hMG & uFSH without pituitary suppression (n = 6) **Arm 3:** long agonist plus hMG & uFSH (n = 6) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis:** none

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Ashkenazi 1989 *(Continued)*

Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not found) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated howeve only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unc ar risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Ashrafi 2005

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English

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Ashrafi 2005 *(Continued)*

	Setting: single centre
	Recruitment period: June 2003 to July 2004
	Sample size (total randomised): 154
Participants	**Inclusion criteria:** at least one previous attempt with low response; baseline FSH >15 mIU/ml; oestradiol concentration on the day of hCG <500 pg/ml; previous cycle with fewer than 3 preovulatory follicles >16 mm
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: predicted low response
	Oocyte donors: no
	Cause of infertility: low ovarian reserve
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** hMG without pituitary suppression (n = 45)
	Arm 2: long agonist plus hMG (n = 52)
	Arm 3: clomifene citrate without pituita y sup ression (n = 34)
	Fertilisation method: ICSI
	Embryo age at the time of transfe unstated
	Luteal phase support: intramuscula progesterone
Outcomes	**Outcomes reported:** cancellation
	Outcomes include in the meta-analysis: none
Notes	**Type of public t on:** published full-text manuscript
	Trial r gistra on: unstated
	Registr i n date: -
	Conflict of interest declaration: unstated
	F ding: unstated
	Au hor correspondence: none undertaken (author contact details not found)
	Calculations used to obtain absolute event numbers: yes
	Inclusion in meta-analysis: no (unclear risk of selection bias; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomization was performed", methodology unstated.

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Ashrafi 2005 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but po sible to ex act absolute event numbers. Cancellation rates expressed in percent ges. Seventeen cycles cancelled in the hMG alone group; 27 in the GnRH ag nist plus hMG group; and 15 in the clomifene citrate plus hMG group. A trition >10% in all trial groups.
Selective reporting (reporting bias)	Low risk	Trial conducted and pub ished pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms No other biases detected.

Ashrafi 2005a

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recrui ment eriod:** nstated **Sampl siz (total randomised):** 60
Participants	**Inclusion criteria:** PCOS (Adams criteria) **Ex lusion criteria:** unstated **Predicted response as stated by the trialists:** predicted high response **Oo yte donors:** no **Cause of infertility:** PCOS **Subgroup (age):** yes (<35 years) **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 30) **Arm 2:** short antagonist plus hMG (n = 30)

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Ashrafi 2005a *(Continued)*

	Fertilisation method: unstated **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - info@royaninstitu e.org (15 S ptember 2021) **Calculations used to obtain absolute event numb rs:** no **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support f judg ment
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not performed. A total of eight cases were lost to follow-up (5 in the agonist group and 3 in the antagonist group). Attrition rate >10% in both trial arms.
Selective reporting (- porting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Ashrafi 2011

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** January 2006 to December 2008 **Sample size (total randomised):** 90
Participants	**Inclusion criteria:** PCOS (Rotterdam criteria); normal uterine cavity; p tent tubes diagnosed by hysterosalpingogram, laparoscopy or hysteroscopy; normal semen an lysis according to WHO criteria. **Exclusion criteria:** previous IVF or ICSI cycles; gonadotrophin reatment for ovarian stimulation within the previous three months **Predicted response as stated by the trialists:** p edicted hig response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n 30) **Arm 2:** long agonist plus rFSH & uhCG (n = 60) - two arms merged (see additional comments) **Fertilisation method** ICSI **Embryo age at the ime of t ansfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outc mes reported:** clinical pregnancy; multiple pregnancy; oocyte number; number of embryos cryopreser ed **Outcomes inc uded in the meta-analysis:** clinical pregnancy; multiple pregnancy; oocyte number; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript **Tria registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - kiani.kiandokht@gmail.com (23 February 2022) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases)

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Ashrafi 2011 *(Continued)*

	Additional comments: A total of 90 women with PCOS undergoing a long agonist protocol were randomised to receive rFSH alone (group A, n = 30), rFSH plus 100 IU hCG (group B, n = 30) or rFSH plus 200 IU hCG (group C, n = 30). For the purposes of meta-analysis, groups B and C were merged into one.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"block randomization technique (…) using a permuted block design. The block lengths were 6. (…) A computerized random number sequence was generated by the statistician".
Allocation concealment (selection bias)	Low risk	"Using each number in the random number sequence in turn selected the next block, determining the next six participant a locations The physician responsible for patient visits allocated the next vailable number upon entry into the trial". The authors confirmed via email (28/0 /2022) that allocation concealment was performed by central alloca ion without the involvement of a trial investigator.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated if participants blinded. "Ou come assessors including laboratory technicians and data analys s wer blinded to group assignment". Only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Outcome assessors in luding laboratory technicians and data analysts were blinded to gro p assignment". Only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analys s ot st ictly performed but possible to obtain absolute event numbers. A trition 10% in group C.
Selective reporting (reporting bias)	Low risk	Selec ive reporting not detected.
Other bias	Low risk	Single centre study with plausible recruitment rates. Trial conducted pre-2010.

Avrech 2004

Study characteristics

Methods	**Des gn:** randomised controlled trial **Cou try:** Israel **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 219
Participants	**Inclusion criteria:** age 40-48 years; regular menstrual cycles (21–35 days); baseline serum FSH level (on day 2 of the current cycle) <15 mIU/mL; BMI <25 kg/m^2; normal baseline endocrine profile (LH, TSH, testosterone, dehydroepiandrosterone sulphate); no history of low ovarian response to stimulation; both ovaries visualised on ultrasound, with no evidence of PCOS or ovarian cyst; uterine cavity normal on hysteroscopy

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Avrech 2004 *(Continued)*

	Exclusion criteria: unstated
	Predicted response as stated by the trialists: predicted low response
	Oocyte donors: no
	Cause of infertility: low ovarian reserve
	Subgroup (age): no
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** hMG without pituitary suppression (n = 73)
	Arm 2: agonist flare plus hMG (n = 146) - two arms merged (see additional comments)
	Fertilisation method: unstated
	Embryo age at the time of transfer: cleavage st ge (days 2-
	Luteal phase support: hCG and progesterone
Outcomes	**Outcomes reported:** live birth; cancellation; oocyte number
	Outcomes included in the meta-analysi live b rth
Notes	**Type of publication:** published full-text m nu cript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declarati n: uns ated
	Funding: unstated
	Author correspond nc : none undertaken (author contact details not found)
	Calculations us d to ob ain absolute event numbers: no
	Inclusi n in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [liv birth and/or OHSS])
	Additiona comments: Patients were randomly allocated to one of three short follicular COS protocols: menotrop ns only (group A, n = 73), menotropins plus a minidose of GnRH agonist (group B, n = 73) or menotropins plus a standard dose of a GnRH agonist (group C, n = 73). Although this was a three-ar trial, for the purposes of meta-analysis groups B and C have been merged.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence g nera-tion (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (perfor-mance bias)	Low risk	Unstated, however only objective outcomes reported.

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Avrech 2004 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Low attrition rates (<10%) in all three arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study Recruitment rates plausible over two years, although trial timeline no specified. Effect size difference lower than two-fold between trial arms No othe biases detected.

Aydin 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Turkey **Language:** English **Setting:** single centre **Recruitment period:** unstate **Sample size (total randomis d)** 60
Participants	**Inclusion criteria:** nstated **Exclusion criter a:** unstated **Predicted response s stated by the trialists:** unstated **Oocyt donors:** no **Cause of infer ility:** various **Subgroup (age):** no **S bgro p (BMI):** no **Sub roup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 30) **Arm 2:** long agonist plus rFSH (n = 30) **Fertilisation method:** unstated **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** ongoing pregnancy; oocyte number; number of cleavage-stage embryos

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Aydin 2012 *(Continued)*

	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - aydin.yunus@yahoo.com (15 September 2 21) **Calculations used to obtain absolute event numbers:** yes **Inclusion in meta-analysis:** no (unclear risk of selection and othe biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Open l bel", however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Op n label", however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis not strictly performed but possible to extract absolute event numbers from percentages. Loss to follow-up not mentioned.
Selective reporting (reporting bias)	Unclear risk	Trial published post-2010, however timeline not stated. Registration status unclear.
Other bias	Unc ear risk	Trial published post-2010, however timeline not stated.

Aydin 2014

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Turkey **Language:** English

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Aydin 2014 *(Continued)*

	Setting: single centre
	Recruitment period: June 2010 to June 2012
	Sample size (total randomised): 80
Participants	**Inclusion criteria:** age 23-35 years; absence of any apparent abnormality of female reproductive system as revealed by medical history and clinical examinations; absence of any metabolic–endocrine system associated diseases; day-3 basal ultrasonography and day-3 hormone profile showing FSH <10 mIU/ml, estradiol <40 pg/ml and AFC >6; male factor or unexplained infertility
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 40)
	Arm 2: short antagonist plus rFSH (n = 40)
	Fertilisation method: ICSI
	Embryo age at the time of transf r: cleav ge stage (days 2-4)
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** cli ical pregnancy; oocyte number
	Outcomes included n the meta-analysis: none
Notes	**Type of publicat on:** publi hed full-text manuscript
	Trial re str tion: nstated
	Regi ration date: -
	Conflict of i terest declaration: none declared
	Funding: unstated
	Autho correspondence: yes - aydin.yunus@yahoo.com (15 September 2021)
	Calc lations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random numbers".

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Aydin 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow p.
Selective reporting (reporting bias)	Unclear risk	Trial conducted post-2010 Regis ration imeline unstated.
Other bias	Unclear risk	Trial conducted post-2010 Registra ion timeline unstated.

Baart 2007

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** The Netherlands **Language:** English **Setting:** single centr **Recruitment period** December 2002 to August 2005 **Sample size (tot l randomised):** 111
Participants	**Inclu ion cri eria:** age <38 years; partner with a sperm count >5 million progressively motile sperm per milli tr (prior to capacitation); regular menstrual cycles (25-35 days), BMI 19-29 kg/m^2; no known chromosom l abnormalities; no relevant systemic disease or uterine and ovarian abnormalities; no history of recurrent miscarriage; no previous IVF cycles not resulting in an embryo transfer **Ex usion criteria:** unstated **Pre icted response as stated by the trialists:** unstated **Oo yte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 44) **Arm 2:** short antagonist plus rFSH (n = 67)

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Baart 2007 *(Continued)*

	Fertilisation method: IVF
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** ongoing pregnancy; oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscript
	Trial registration: NCT00985062
	Registration date: 28 September 2009
	Conflict of interest declaration: unstated
	Funding: "This research was financially supported by h Erasmus University (AIO) and the 'Stichting Voortplantingsgeneeskunde Rotterdam'."
	Author correspondence: none undertaken
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (high risk of other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support f judg ment
Random sequence generation (selection bias)	Low risk	"Ran omiza ion to one of the two treatment groups was performed according to a computer generated randomisation schedule".
Allocation concealment (selection bias)	Low risk	"Numbered sealed envelopes", opened sequentially.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed, but 16% attrition between randomisation and oocyte retrieval in the mild stimulation group versus 9% in the conventional stimulation group.
Selective reporting (- porting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	High risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. The study was "terminated prematurely, after an unplanned interim analysis (…) found a lower embryo aneuploidy rate following mild stimulation."

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Badrawi 2005

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Egypt **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 100
Participants	**Inclusion criteria:** age 18-39 years; regular menstrual cycle; FSH level <10 IU/ done on cycle day 3; ultrasound examination showing normal uterus **Exclusion criteria:** severe endometriosis (American Fertility Society stages III and IV); male partners with azoospermia **Predicted response as stated by the trialists:** u stated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 50) **Arm 2:** short antagonist plus hMG (n = 50) **Fertilisation method** ICSI **Embryo age at the ime of t ansfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outc mes reported:** OHSS; miscarriage; oocyte number **Outcomes ncluded in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial gistration:** unstated **Regi tration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - kaainih@link.net (15 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

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Badrawi 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes" but unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes repo ted.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly pe formed but possible to extract absolute event numbers. Three participants lost in the short antagonist group due to cycle cancellation (low response) Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted a d publ shed pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted and published pre-2010. Single centre study. Duration of the trial not s ated, th refore unclear whether recruitment rates were appropriate.

Bahceci 2005

Study characteristics

Methods	**Design:** random sed controlled trial **Country:** Tur y **Language:** English **Setting:** single centre **R cruitment period:** November 2001 to November 2002 **Sample size (total randomised):** 148
Participants	**Inclusion criteria:** PCOS **Exclusion criteria:** previous ART; hyperprolactinaemia or thyroid abnormalities **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no

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Bahceci 2005 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG & uFSH (n = 75) **Arm 2:** short antagonist plus hMG & uFSH (n = 73) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** OHSS; multiple pregnancy; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - mbahceci@ peronline.com (15 September 2021) **Calculations used to obtain absolute ev nt numbers:** yes **Inclusion in meta-analysis:** yes (sensit vity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS] **Additional comments:** -

Risk of bias

Bias	**Authors' judgemen**	**upport for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table".
Allocation concealment (selection bias)	Uncl r risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Un lear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detec ion bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. A total of 5 participants dropped out from the GnRH agonist group, and 14 from the antagonist group. Therefore attrition rate >10% in one of the trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Bahceci 2005 *(Continued)*

Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Baker 2009

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** multicentre **Recruitment period:** February 2005 to May 2006 **Sample size (total randomised):** 152
Participants	**Inclusion criteria:** age 18–39 years, BMI 18–30 kg/m^2, <3 prior oocyte retrievals; basal FSH <10 IU/l and estradiol <80 pg/ml; >10 antral follicles 2–10 mm in size; uterine cavity consistent with normal expected function as assessed through hysterosalpingogram, sonohysterography or hysteroscopy within 12 months of beginning the study; normal or clinically insignificant hematology and blood chemistry values; normal TSH level or euthyroid as determined by the investigator **Exclusion criteria:** POI; previous low response; previous OHSS; PCOS; one or both ovaries inaccessible for oocyte retrieval; persistent ovarian cysts >20 mm; untreated hydrosalpinx; stages III-IV endometriosis; oocyte donation; contraindications to pregnancy; abnormal bleeding of undetermined origin; uncontrolled thyroid or adrenal dysfunction, neoplasia, severe impairment of renal or hepatic function; use of concomitant medications **Predicted response as stated by the trialists:** unselected population **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus uFSH (n = 76) **Arm 2:** long agonist plus rFSH (n = 76) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** various **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; cancellation; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** live birth; clinical pregnancy; cancellation; oocyte number; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript

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Baker 2009 *(Continued)*

Trial registration: unstated

Registration date: -

Conflict of interest declaration: "Dr. Baker has received research support from IBSA. Dr. Adamson is CEO and Shareholder of Advanced Reproductive Care, is a physician owner of Fertility Physicians of Northern California, has received research support from IBSA, and has been a speaker for Ferring Pharmaceuticals. His spouse is also a shareholder in Advanced Reproductive Care. Dr Hoehler has served as a consultant to IBSA, Vital Therapies, Inc., Pioneer Surgical, Kyphon, Cooper Surgical, and Fziomed. Dr. Jones is a consultant for VitalTherapies, Inc., and IBSA, and as of 7/1/07, became an employee of IBSA. Drs. Fujimoto, Kettel, and Soules report no conflicts of interest."

Funding: "Institut Biochimique SA (IBSA), Switzerland."

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: yes

Inclusion in meta-analysis: yes (primary analysis - low risk of s lection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-genera ed ra domization".
Allocation concealment (selection bias)	Low risk	"Sealed e velope containing the randomization number on the exterior and tre tment a signment in the interior were provided".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open label s udy, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Op n label study, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low ri k	ITT analysis performed. Six women cancelled in the uFSH group and five in the rFSH group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Lo risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low isk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Balasch 1996

Study characteristics

Methods	**Design:** randomised controlled trial
	Country: Spain

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Balasch 1996 *(Continued)*

	Language: English
	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 188
Participants	**Inclusion criteria:** age 23-39 years; serum FSH <12 mIU/ml
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus uFSH (n = 92)
	Arm 2: long agonist plus hMG & uFSH (n = 96)
	Fertilisation method: unstated
	Embryo age at the time of transf r: unstated
	Luteal phase support: hCG or prog tero e
Outcomes	**Outcomes reported:** clinical pregnancy; multiple pregnancy; oocyte number
	Outcomes included in the me analysis: none
Notes	**Type of publicatio** publis ed full-text manuscript
	Trial registration: unstated
	Registration ate: -
	Conflic of nterest declaration: unstated
	Funding: unst ted
	Au hor correspondence: none undertaken (author contact details not found)
	C lcula ions used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation table".

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Balasch 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow p.
Selective reporting (reporting bias)	Low risk	Trial conducted and published p 2010 Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single ce tre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Balasch 2001

Study characteristics	
Methods	**Design:** randomised controll d trial **Country:** Spain **Language:** English **Setting:** single centr **Recruitm t peri d:** unstated **Samp e size otal randomised):** 30
Participants	**Inclusion cr teria:** age 29–40 years; regular menstrual cycles; both ovaries present; serum FSH <11 IU/l **Exclusion criteria:** PCOS; ≤2 previous ART cycles **Predi ted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 14) **Arm 2:** long agonist plus rFSH & rLH (n = 16) **Fertilisation method:** IVF or ICSI

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Balasch 2001 *(Continued)*

	Embryo age at the time of transfer: unstated
	Luteal phase support: hCG
Outcomes	**Outcomes reported:** oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: "Recombinant FSH and LH were kindly provided b Ares- erono International S.A., Geneva, Switzerland."
	Author correspondence: yes - jbalasch@medicin .ub.es (15 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support or j dgement
Random sequence generation (selection bias)	Low risk	"comput r-generated randomization table"
Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes were used", although unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	nstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Attrition rate <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Balasch 2003

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 60
Participants	**Inclusion criteria:** age 26-37 years; regular menstrual cycles (27–33 days); BM 18–25 kg/m^2; both ovaries present; cycle day 3 FSH concentration <10 IU/l **Exclusion criteria:** PCOS; hormonal therapy within th previous six months **Predicted response as stated by the trialists:** u stated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (=30) **Arm 2:** long agonist plus hMG (n = 30) **Fertilisation method:** ICSI **Embryo age at the ime of ransfer:** cleavage stage (days 2-4) **Luteal phase support:** G
Outcomes	**Outcomes re orted:** OHSS; clinical pregnancy; miscarriage; oocyte number; number of cleavage-stage embr os; number of embryos cryopreserved **Outcomes cluded in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial r gistration:** unstated **Regi tration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - jbalasch@medicina.ub.es (15 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

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Balasch 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated table".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes repo ted.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Embryology assessors blinded, rest nstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly pe formed but possible to extract absolute event numbers. Attrition rate >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted a d publ shed pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study tim lin uns ated. Effect size difference lower than two-fold between trial arms No the biases detected.

Barmat 2005

Study characteristics

Methods	**Design:** n omised controlled trial **Coun ry:** Un ed States of America **Language:** nglish **Se ting:** multicentre **Recru tment period:** unstated **Sample size (total randomised):** 80
Participants	**Inclusion criteria:** age <39 years; day 3 FSH level of ≤10 (units unstated) and oestradiol level of <60 pg/ml; basal AFC >5; regular menstrual cycles (26-34 days); ≤1 previous failed IVF or IVF/ICSI cycle; BMI 19-32 kg/m^2; no hydrosalpinx present by hysterosalpingogram, laparoscopy, or ultrasound within the past year **Exclusion criteria:** previous low response; fertility medications within the previous month **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various

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Barmat 2005 *(Continued)*

	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 41)
	Arm 2: short antagonist plus rFSH (n = 39)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: various
	Luteal phase support: progesterone (variable route)
Outcomes	**Outcomes reported:** live birth; OHSS; ongoing pregnancy; multiple pregnancy; oocyte number; number of embryos cryopreserved
	Outcomes included in the meta-analysis: live bi th; OHSS
Notes	**Type of publication:** published full-text manuscri t
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - lba mat@a ington-repromed.com (15 September 2021)
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comme ts:

Risk of bias

Bias	Autho s' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear ris	"sealed randomization envelopes".
Allocation concealment (selection bias)	Un lear risk	"Sealed envelopes", although unclear if SNOSE.
Blinding of particip nts and personnel (p rformance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Four women lost to follow-up (four in the antagonist group and one in the agonist group). Attrition = 10% in the antagonist group.

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Barmat 2005 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Barrenetxea 2008

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** January to June 2005 **Sample size (total randomised):** 84
Participants	**Inclusion criteria:** low ovarian response (diagnosed when both factors, age >40 years and elevated day 3 FSH level >10 mIU/ml, were present); prese of both ovaries **Exclusion criteria:** low-responding wome aged <40 years and with normal basalFSH levels **Predicted response as stated y the ialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI)** no **Subgroup (et nicity)** no
Interventions	**Arm 1:** agonist flare plus rFSH & rLH (n = 42) **Arm 2:** agonist flare plus rFSH (n = 42) **Fe ilisation method:** ICSI **Em ryo age at the time of transfer:** cleavage stage (days 2-4) **Lut al phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** cancellation; oocyte number **Outcomes included in the meta-analysis:** cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated

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Barrenetxea 2008 *(Continued)*

Funding: unstated

Author correspondence: yes - gorkabz@euskalnet.net (15 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation.
Allocation concealment (selection bias)	Low risk	"Sealed envelopes used", cent ally ma aged by a nurse who "assigned partici-patns to their groups and was responsible for coding protection.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding undertaken.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjecti e out mes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analys s unde taken. Eight cycles cancelled in total (4 in each group). Attrition ra <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial c nducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Barriere 1987

Study characteristics

Methods	**Des n:** randomised controlled trial **untry:** France **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 60
Participants	**Inclusion criteria:** unstated **Exclusion criteria:** unstated

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Barriere 1987 *(Continued)*

	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** clomifene citrate plus hMG without pituitary suppression (n = 30)
	Arm 2: long agonist plus hMG (n = 30)
	Fertilisation method: unstated
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** clinical pregnancy; oocyte nu ber; number of cleavage-stage embryos
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text m nuscr pt
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: uns ated
	Funding: unstated
	Author correspondence: none u dertaken (author contact details not found)
	Calculations used t ob ain absolute event numbers: yes
	Inclusion in meta-analy s: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Addit onal comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	U clear isk	"randomly assigned".
Allocation conce lment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.

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Barriere 1987 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear whether ITT analysis performed for some outcomes (e.g. ongoing pregnancy rate, with total even numbers calculated from percentages). A total of 10 cancellations in the clomifene citrate and hMG group. Attrition >10% in one trial arm.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold betw en trial arms.

Baruffi 1999

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Brazil **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 120
Participants	**Inclusion criteria:** age ≤37 years **Exclusion criteria:** unstated **Predicted response as stated b the trialists:** unstated **Oocyte donors:** no **Cause of inferti ty:** un t ted **Subgro p (a e):** no **Subg oup (BMI):** no **Subgroup (e hnicity):** no
Interventions	**Arm 1:** rFSH without pituitary suppression (n = 60) **A m 2:** FSH without pituitary suppression (n = 60) **Fert isation method:** ICSI **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** severe OHSS; clinical pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated

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Baruffi 1999 *(Continued)*

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: none undertaken (author contact details not found)

Calculations used to obtain absolute event numbers: yes

Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"in a randomized manne ".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, howeve o ly objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, h wever only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not performed. Absolute event numbers extracted from percentages.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear isk	Trial conducted and published pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated.

Basly 2012

Study characteris cs

Methods

Design: randomised controlled trial

Country: Tunisia

Language: English

Setting: single centre

Recruitment period: November 2004 to February 2008

Sample size (total randomised): 220

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Basly 2012 *(Continued)*

Participants	**Inclusion criteria:** age 18-39 years; PCOS; no endometriotic cyst; basal serum FSH normal **Exclusion criteria:** previous low ovarian response **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 110) **Arm 2:** short antagonist plus rFSH (n = 110) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2 4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; o going pregnancy; cancellation **Outcomes included in the meta-analysis** cli ical pregnancy; ongoing pregnancy; cancellation
Notes	**Type of publication:** published fu -text m nuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calcul tions sed to obtain absolute event numbers:** no **Inclusio i meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence gene a-tion (selection b s)	Low risk	"computer generated randomization list".
Allocation concealment (selection bias)	Low risk	"performed by a study nurse".
Blinding of participants and personnel (perfor-mance bias) All outcomes	High risk	"Neither patients nor doctors were blinded to the treatment assigned", subjec-tive outcomes reported.

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Basly 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	"Neither patients nor doctors were blinded to the treatment assigned", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Five cancellations in the agonist group and four in the antagonist group. Loss to follow-up <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single cent e study with lausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases dete ted.

Bastu 2016

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Turkey **Language:** English **Setting:** single centre **Recruitment period:** Novemb r 201 t August 2015 **Sample size (total randomis d):** 95
Participants	**Inclusion criteria:** age 18-42 years; low-responding women (Bologna criteria); regular menstrual cycles (25-34 days); BMI 19 3-28 9 kg/m^2; no metabolic or endocrine disorders; normal hormone panel; ICSI cycle with ejaculate s erm normal uterus documented by HSG or hysteroscopy **Exclusion crite :** previous cytotoxic chemotherapy and/or radiotherapy; history of ovarian surgery such as oph rectomy or cystectomy; history of DHEA and/or testosterone supplement use; natural IVF **Predi ted r sponse as stated by the trialists:** predicted low response **Oocyte don rs:** no **Cause of infertility:** various **Subgr up (age):** no **Sub roup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH & hMG (n = 62) - two arms merged (see additional comments) **Arm 2:** short antagonist plus letrozole & rFSH & hMG (n = 33) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone

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Bastu 2016 *(Continued)*

Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT02293668 **Registration date:** 10 June 2016 **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - ercan.bastu@istanbul.edu.tr (15 Sep ember 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selec ion bias [a ocation concealment unstated]; primary review outcomes not reported) **Additional comments:** A total of 95 women were andomly a signed to one of three groups. In the first group, 31 patients were treated with 450 IU gonadotr pins In the second group, 31 patients were treated with 300 IU gonadotropins. The third group included 33 patients who were treated with 150 IU gonadotropins in combination with letrozole. Fo the purposes of meta-analysis, we planned to amalgamate groups 1 and 2.

Risk of bias

Bias	Authors' judgement	Support or judg ment
Random sequence generation (selection bias)	Low risk	"compu er-generated sequence".
Allocation concealment (selection bias)	Unclear risk	"Sealed nvelopes were used for the randomization list", although unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The infertility specialist (E.B.) who was blinded observed follicular development using ultrasound and retrieved oocytes in all participating patients. The embryologist (S.B.) was also blinded to the assigned treatment protocol."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The infertility specialist (E.B.) who was blinded observed follicular development using ultrasound and retrieved oocytes in all participating patients. The embryologist (S.B.) was also blinded to the assigned treatment protocol."
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. A total of 25 women were cancelled (nine in group 1, eight in group 2, and eight in group 3). Attrition >10% in all trial arms.
Selective reporting (- porting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

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Battaglia 2000

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 46
Participants	**Inclusion criteria:** age <38 years; tubal infertility; regular menstrual cycles (28 ± 4 days); normal SFA (WHO standards); serum FSH <15 IU/l and oestradiol levels <200 pmol/l on day 3 of the menstrual cycle; normal uterine cavity **Exclusion criteria:** concurrent illness; BMI >30 kg m^2; endometriosis; ovarian functional cysts; PCOS; smoking (>10 cigarettes/day); hypertension **Predicted response as stated by the trialists:** uns ted **Oocyte donors:** no **Cause of infertility:** tubal **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & uFSH (n = 23) **Arm 2:** long agonist plus uFSH (n 23) **Fertilisation meth d:** unsta ed **Embryo age at the time f transfer:** cleavage stage (days 2-4) **Luteal hase suppor :** vaginal progesterone
Outcomes	**Outcom s eported:** OHSS; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Tri l registration:** unstated **Reg stration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not found) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

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Battaglia 2000 *(Continued)*

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random number table".
Allocation concealment (selection bias)	Low risk	."Sequentially sealed envelopes containing tratment allocation determined by a random number table".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective out omes rep rted.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Seven cycles cancelled in total (three in group one, and four in group two). Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted d published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial cond ted p e-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms.

Begueria 2019

Study characteristics

Methods	**Design:** rand mised controlled trial **Country:** Spain **La guage:** English **Setti g:** single centre **Rec itment period:** June 2016 to June 2017 **mple size (total randomised):** 216
Participants	**Inclusion criteria:** age 18-35 years old; first cycle of oocyte donation; normal ovarian morphology on transvaginal ultrasound; AFC >8 **Exclusion criteria:** irregular menstrual cycles; any hormonal treatment in the previous 3 months; serum oestradiol levels >70 pg/ml on day 2 of the menstrual cycle **Predicted response as stated by the trialists:** unstated **Oocyte donors:** yes **Cause of infertility:** N/A

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Begueria 2019 *(Continued)*

	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** progestogen plus rFSH (n = 97)
	Arm 2: short antagonist plus rFSH (n = 97)
	Fertilisation method: N/A
	Embryo age at the time of transfer: N/A
	Luteal phase support: N/A
Outcomes	**Outcomes reported:** cancellation
	Outcomes included in the meta-analysis: cancellati
Notes	**Type of publication:** published full-text manusc pt
	Trial registration: NCT02796105
	Registration date: 10 June 2016
	Conflict of interest declaration: none de ared
	Funding: "Completely intramurally funded w h no commercial sponsorship or external support of any kind."
	Author correspondence: yes - rva sena@eugin.es (21 February 2021)
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)
	Additional comments: -

Risk of bias

Bias	Authors jud emen	Support for judgement
Random sequence generation (selection bias)	Low ris	"computer-generated sequence".
Allocation concealment (selection bias)	Low risk	"allocation performed by a pharmacist using a password protected programme".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants and physicians were not blinded to group assignment", however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"the main investigator (R.B.) and those involved in data compilation and statistics (D.G., F.F., S.B.) were blinded during the outcomes assessment and statistical analysis, respectively.". Only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Three women cancelled in the progesterone group and four in the GnRH antagonist group. Attrition <10% in both groups.

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Begueria 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	Prospectively registered study. Outcomes reported as per protocol.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Benadiva 1988

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** single centre **Recruitment period:** January to June 1987 **Sample size (total randomised):** 110
Participants	**Inclusion criteria:** normal ovulatory women suffering from mechanical causes of infertility **Exclusion criteria:** unstated **Predicted response as stated by h tria sts:** unstated **Oocyte donors:** no **Cause of infertility:** tubal **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethni ity):** no
Interventions	**Arm** hMG uFSH without pituitary suppression (n = 54) **Arm 2:** hMG without pituitary suppression (n = 56) **Fe tilisation method:** unstated **Embryo age at the time of transfer:** unstated **Lute l phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number; number of cleavage-stage embryos **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated

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Benadiva 1988 *(Continued)*

Funding: unstated

Author correspondence: none undertaken (author contact details not found)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only obje tive outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, howe er only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT ana ysis not performed. Attrition >10%.
Selective reporting (reporting bias)	Low risk	T ial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Beretsos 2009

Study characteristics

Methods	**Des gn:** randomised controlled trial **Country:** Greece **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 50
Participants	**Inclusion criteria:** age 25-40 years; normal hormonal profile (WHO guidelines); no ovulation induction or any other hormone treatment for at least three months preceding the study

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Beretsos 2009 *(Continued)*

	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 28)
	Arm 2: long agonist plus rFSH & uhCG (n = 22)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: hCG
Outcomes	**Outcomes reported:** oocyte number
	Outcomes included in the meta-analysis none
Notes	**Type of publication:** published full-text manu cript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declarati n: none declared
	Funding: unstated
	Author correspond nce: ye - pberet@biol.uoa.gr; partsiobgyn@yahoo.com (15 September 2021)
	Calculations us d to o in absolute event numbers: no
	Inclusion in eta-a alysis: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Additiona comments: -

Risk of bias

Bias	Autho s' judgement	Support for judgement
Random sequence enera tion (selection bias)	Low isk	Online "random number generator."
Allocation concealm nt (selection bias)	Unclear risk	"a random number was generated and the patient was allocated to the corresponding group".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias)	Low risk	Unstated, however only objective outcomes reported.

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Beretsos 2009 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not performed. One patient dropped out from the rFSH group, and three dropped out from the hCG group. Attrition >10% in the hCG group.
Selective reporting (reporting bias)	High risk	Trial conducted pre-2010. No report on clinical pregnancy rates despite methods describing this outcome.
Other bias	Unclear risk	Trial conducted pre-2010. Effect size difference lower than two-fold between trial arms. No other biases detected. Single cen re study. Recruitment rates unclear as study timeline unstated.

Berger 1999

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Switzerland **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total random sed):** 48
Participants	**Inclusion criteria:** age 18-39 years; r gular menstrual cycles; BMI 18-29 kg/m^2 **Exclusion criteria:** unstated **Predicted response as stat d by the trialists:** unstated **Oocyte donors:** o **Cause o inf rtility** unstated **Subg oup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**A m 1:** l ng agonist plus rFSH (n = 89) **Arm 2:** long agonist plus uFSH (n = 76) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** OHSS; cancellation; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** conference abstract

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Berger 1999 *(Continued)*

Trial registration: unstated

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: none undertaken (author contact details not found)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Open study", ho ever only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Ope study however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Ana ysis per cycle.
Selective reporting (reporting bias)	Low ri k	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Bergh 1997

Study characteristics

Methods

Design: randomised controlled trial

Country: International (Sweden, Switzerland)

Language: English

Setting: multicentre

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Bergh 1997 *(Continued)*

	Recruitment period: December 1995 to September 1996
	Sample size (total randomised): 235
Participants	**Inclusion criteria:** age 18-38 years; regular menstrual cycles (25-35 days); AFC >10 per ovary; tubal factor, mild endometriosis (classification stage I or II of the American Society of Reproductive Medicine), male factor unexplained infertility; ≤3 previous assisted reproduction attempts; presence of both ovaries and a normal uterine cavity; willingness to participate and comply with the protocol for the duration of the study
	Exclusion criteria: BMI >28 kg/m^2; previous OHSS; previous low response to gonadotrophin therapy defined as <3 mature follicles; male azoospermia or semen infection
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 119)
	Arm 2: long agonist plus uFSH (n = 116)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of ransfer cleavage stage (days 2-4)
	Luteal phase support: hCG and progesterone
Outcomes	**Outcomes reported:** OHSS; ngoing pregnancy; multiple pregnancy; miscarriage; oocyte number; number of cleavage-stag embryos; number of embryos cryopreserved
	Outcomes included in the meta-analysis: OHSS
Notes	**Type of publicati n:** published full-text manuscript
	Trial egistra ion: unstated
	Registrati n date: -
	Co flict of interest declaration: unstated
	Fun ing: unstated
	Author correspondence: none undertaken (author contact details not found)
	C culations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

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Bergh 1997 *(Continued)*

Random sequence generation (selection bias)	Low risk	" computer-generated 1:1 randomization list".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Physicians blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Assessor-blind study".
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed, ut possible to extract absolute event numbers. No cycle cancella ions n the rFSH group; 12 women cancelled in the uFSH group. Attrition >10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and publi hed pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size d fference lower than two-fold between trial arms. No other biases detected.

Berkkanoglu 2007

Study characteristics	
Methods	**Design:** randomised c trolled trial **Country:** Turkey **Language:** Engl h **Setting:** singl centre **Recruitm nt period:** unstated **Sample size (total randomised):** 145
Participants	**Incl sion criteria:** AFC <12 **Excl sion criteria:** age >42 years; only one ovary; basal serum FSH >12 IU/l **edicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus rFSH (n = 51)

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Berkkanoglu 2007 *(Continued)*

	Arm 2: agonist flare plus rFSH & rLH (n = 46) **Arm 3:** agonist flare plus rFSH & rhCG (n = 48) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - mberkkan@hotmail.com (15 September 2021) **Calculations used to obtain absolute ev nt numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	**Authors' judgement**	**Suppor for judgement**
Random sequence generation (selection bias)	Unclear risk	Uns ated.
Allocation concealment (selection bias)	Unclear ri k	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear r	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Un lear risk	Unstated, subjective outcomes reported.
Incomplete outco e data (attrition bias) All outcomes	High risk	ITT analysis not performed. CPR calculated takinginto account the total cancelled cycles (cancelled COH + ET), then subtracting from this the cancelled COHSnumber. This was the number of transfers per group. Then used the percentage in table 3 to determine the number of CP per group based on CPR per transfer. Seven women cancelled in group A, five in group B and five in group C. Attrition >10% in at least one of the trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Berkkanoglu 2007 *(Continued)*

Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Blasco 2017

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** unstated **Language:** English **Setting:** single centre **Recruitment period:** September 2015 to Januar 2017 **Sample size (total randomised):** 82
Participants	**Inclusion criteria:** low ovarian reserve; first IVF cycle **Exclusion criteria:** unstated **Predicted response as stated by the t alists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian res rve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicit):** no
Interventions	**Arm 1:** short ant gonist plus rFSH & hMG (n = 43) **Arm 2:** agonis flare plus rFSH & hMG (n = 39) **Fertili atio method:** unstated **Embryo age the time of transfer:** unstated **Lu eal phase support:** unstated
Outcomes	**O tcomes reported:** oocyte number; number of embryos cryopreserved **Out omes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken

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Blasco 2017 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (insufficient data from the abstract for quantitative analysis, no contact details found for the study authors)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if ITT analysi erformed.
Selective reporting (reporting bias)	Unclear risk	Unable to assess reporting bias.
Other bias	Unclear risk	Single centre study with plausible recruitment rates. Registration status unclear.

Bodri 2006

Study characteristics

Methods	**De ign:** randomised controlled trial **Coun ry:** Spain **Language:** English **tting:** single centre **Recruitment period:** August 2004 to May 2005 **Sample size (total randomised):** 118
Participants	**Inclusion criteria:** age of oocyte donors 18-30 years; BMI <30 kg/m^2; regular menstrual cycles (26–36 days); normal basal FSH and LH levels **Exclusion criteria:** donors with previous history of low response to ovarian; PCOS **Predicted response as stated by the trialists:** unstated

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Bodri 2006 *(Continued)*

	Oocyte donors: yes
	Cause of infertility: N/A
	Subgroup (age): yes (<35 years)
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 60)
	Arm 2: long agonist plus rFSH (n = 58)
	Fertilisation method: N/A
	Embryo age at the time of transfer: N/A
	Luteal phase support: N/A
Outcomes	**Outcomes reported:** oocyte number
	Outcomes included in the meta-analysis: oocyte number
Notes	**Type of publication:** published full-text man script
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: nstated
	Funding: unstated
	Author correspondence: non undertaken
	Calculations used to obtain ab lute event numbers: no
	Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)
	Additional comments:

Risk of bias

Bias	Authors j dgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomization".
Allocation concealment (selection bias)	Low risk	"Sealed opaque envelopes with consecutive numbers".
Blinding of participants and personnel (pe fo mance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias)	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Attrition <10% in both arms.

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Bodri 2006 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Registration unstated. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Borm 2000

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** International **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 701
Participants	**Inclusion criteria:** age at least 18 years but not older than 39 years; BMI 18-29 kg/m^2; regular menstrual cycles (24-35 days) **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility** var ous **Subgroup (age):** no **Subgroup (B I):** yes <30 kg/m^2) **Subgro p (thnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 463) **Ar 2:** long agonist plus rFSH (n = 238) **Fer ilisation method:** IVF or ICSI **Embryo age at the time of transfer:** various **Luteal phase support:** variable
Outcomes	**Outcomes reported:** ongoing pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated

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Borm 2000 *(Continued)*

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: yes - b.mannaerts@organon.ass.akzonobel.nl (15 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice response system.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial, s bj cti e outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label rial
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Twenty-three cycles cancelled in the ganirelix group, and seventeen in the buserelin group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Bosch 2008

Study character stics

Methods

Design: randomised controlled trial

Country: Spain

Language: English

Setting: single centre

Recruitment period: January 2003 to December 2006

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Bosch 2008 *(Continued)*

	Sample size (total randomised): 280
Participants	**Inclusion criteria:** age 18–37 years; regular menstrual cycles (25 to 35 days); BMI <30 kg/m^2; normal basal serum FSH (<10 IU/l) and oestradiol (>75 pg/ml) levels determined on day 3 of the cycle previous to COS; no uterine (fibroids, adenomyosis, congenital malformations), ovarian (endometrioma, polycystic ovaries) or adnexal (hydrosalpinx) abnormalities assessed by vaginal ultrasound **Exclusion criteria:** RPL; systemic disease; endocrine or metabolic disorder; ovulation induction in the previous month **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus hMG (n = 140) **Arm 2:** short antagonist plus rFSH (n = 140) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage tage (days 2-4) **Luteal phase support:** vaginal pr gestero e
Outcomes	**Outcomes reported:** live birth; OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; cancellation; oocyte number; number of emb yos cryopreserved **Outcomes included in the m ta analysis:** live birth; OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; cancellat o oocyte number; number of embryos cryopreserved
Notes	**Type of publication** ublis ed full-text manuscript **Trial registration** NCT00669786 **Regis ration date:** 1 May 2008 **Conflict of nterest declaration:** unstated **Fu ding:** unstated **Auth r correspondence:** none undertaken **Calc lations used to obtain absolute event numbers:** no **lusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.

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Bosch 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	Centralised allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label study, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis stated by the authors and ex acted from the data. Eighteen women cancelled in HP-hMG group; and forte n canc lled in rFSH group. Attrition >10% in one trial arm.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010 Selec e reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single ce tre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Bosch 2011

Study characteristics	
Methods	**Design:** randomised controll d trial **Country:** Spain **Language:** English **Setting:** single centr **Recruitm t peri d:** January 2005 to December 2007 **Samp e size otal randomised):** 720
Participants	**Inclusion cr eria:** age 18-39 years; regular menstrual cycles (25-35 days); BMI body <30 kg/m^2; normal basal serum FSH (<12 IU/l) and oestradiol (>75 pg/ml) on day 3 of the menstrual cycle prior to COS; no uterine (fibroids, adenomyosis, congenital malformations), ovarian (endometrioma, polycystic ovar es), or adnexal (hydrosalpinx) abnormalities assessed by vaginal ultrasound examination **Excl sion criteria:** RPL; systemic disease; endocrine or metabolic disorder; ovulation induction in the prev ous month **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no

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Bosch 2011 *(Continued)*

Interventions	**Arm 1:** short antagonist plus rFSH (n = 360) **Arm 2:** short antagonist plus rFSH & rLH (n = 360) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; cancellation; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** OHSS; cancellation; oocyte number; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - ebosch@ivi es (24 February 2021) **Calculations used to obtain absolute even numbers:** yes **Inclusion in meta-analysis:** yes (pr ma y analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Suppo t for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated lists".
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label, subjective outcomes reported.
Blinding of outcome assessment (detectio bias) All outcomes	High risk	Open label, subjective outcomes reported.
Incomplete outcom data (attrition bias) All outcomes	High risk	ITT analysis performed as stated by the authors. Possible to extract absolute values for reported outcomes. Forty-six women discontinued in the rFSH group, and 49 women discontinued in the rFSH/rLH group. Cancelled: 24 women in rFSH group, and 28 women in the rFSH/rLH group. Overall attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. No details of registration. Selective reporting not detected.

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Bosch 2011 *(Continued)*

Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Brannian 2010

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 8
Participants	**Inclusion criteria:** age <35 years; tubal or male factor infertility **Exclusion criteria:** unstated **Predicted response as stated by the t alists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** yes (<35 yea s) **Subgroup (BMI):** no **Subgroup (ethnicit):** no
Interventions	**Arm 1:** long agonist plus FSH (n = 4) **Arm 2:** long a onist plus hMG (n = 4) **Fertili atio method:** unstated **Embryo age the time of transfer:** unstated **Lu eal phase support:** unstated
Outcomes	**O tcomes reported:** clinical pregnancy; oocyte number **Out omes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** "This research was supported by NIH INBRE 2P20RR016479 and Sanford Research/USD Women's Health Research Center." **Author correspondence:** yes - jbrannia@usd.edu (15 September 2021)

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Brannian 2010 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Prospectively randomised", methodology unsta ed.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis perform Attrition unstated.
Selective reporting (reporting bias)	Low risk	Selective eporting not detected.
Other bias	Unclear risk	Single centre study. Recruitment rates unclear as study timeline unstated.

Bülow 2021

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Denmark **L nguage:** English **Sett ng:** multicentre **Recruitment period:** August 2016 to November 2018 **Sample size (total randomised):** 159
Participants	**Inclusion criteria:** age 18-40 years; BMI <35 kg/m^2; normal ovarian reserve (AMH 8-32 nmol/ml); regular menstrual cycles (21-35 days) **Exclusion criteria:** previous stimulation with <4 oocytes; PCOS (Rotterdam criteria); contraindications to letrozole **Predicted response as stated by the trialists:** predicted normal response

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Bülow 2021 *(Continued)*

	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus letrozole & rFSH (n = 80)
	Arm 2: short antagonist plus rFSH (n = 79)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: various
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** ongoing pregnancy; cance ation; oocy number
	Outcomes included in the meta-analysis: ongoing pregna cy; cancellation; oocyte number
Notes	**Type of publication:** published full-text man script
	Trial registration: NCT02939898 and NCT 29466 4
	Registration date: 15 August 2016
	Conflict of interest declaration: N.S M. r ports grants and personal fees from Merck Serono, Ferring, Anecova and Gedeon Richter, and e sona fees from Institut Biochimique SA (IBSA), Vivoplex, ArtPred and Swiss Precision Diagnostic outsi the submitted work. A.P. reports grants and personal fees from Ferring, Merck and Gedeon R chter, utside the submitted work. The remaining authors declare that they have no competing interests in the research or publication."
	Funding: "The RIOT study was a part of the scientific collaboration ReproUnion, co-financed by the European Union, Inter eg V O¨ KS, and Ferring Pharmaceuticals. Roche Diagnostics contributed financially by providing assays availa le for markers of endocrinology. The funders had no role in designing the study, interpreta ion of the findings or in the publications process."
	Author orrespond nce: none undertaken
	Calcu ation used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequen e ge eration (selection bias)	Low risk	"Identical capsules with letrozole or placebo were prepared by a certified research pharmacy and randomized in blocks of six in a ratio of 1:1 and stored in consecutive, serial numbered containers. The pharmacy delivered the containers directly to the investigator sites accompanied by sealed envelopes."
Allocation concealment (selection bias)	Low risk	"Identical capsules with letrozole or placebo were prepared by a certified research pharmacy and randomized in blocks of six in a ratio of

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Bülow 2021 *(Continued)*

		1:1 and stored in consecutive, serial numbered containers. The pharmacy delivered the containers directly to the investigator sites accompanied by sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Medical staff, patients, investigators and assessors were blinded to treatment allocation until the end of the clinical trial when primary laboratory results had been analysed."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Medical staff, patients, investigators and assessors were blinded to treatment allocation until the end of the clinical trial when primary laboratory results had been analysed."
Incomplete outcome data (attrition bias) All outcomes	High risk	During the trial, 13 and 17 patients were ex luded fro the letrozole and placebo groups, respectively. Attritio 0% in oth trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registr tion undertaken prospectively. All outcomes reported as state in the regis ration.
Other bias	Low risk	Trial conducted post-2010 a d pro pectively registered. Multicentre study. Effect size difference lower than two-fold between trial arms.

Cakiroglu 2013

Study characteristics	
Methods	**Design:** randomised controlled t ial **Country:** Turkey **Language:** English **Setting:** single cent e **Recruitment p iod:** September 2011 to July 2012 **Sample size (otal randomised):** 55
Participants	**Inclusion riteria:** predicted low ovarian response (Bologna criteria) **Ex lusion criteria:** unstated **Predicted response as stated by the trialists:** predicted low response **Ooc te donors:** no **Ca se of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus rFSH & hMG (n = 27) **Arm 2:** short antagonist plus letrozole & rFSH & hMG (n = 28) **Fertilisation method:** ICSI

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Cakiroglu 2013 *(Continued)*

	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - dryigit1@yahoo.com (1 September 2021)
	Calculations used to obtain absolute event nu bers: no
	Inclusion in meta-analysis: no (unclear risk of sele tion an other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support f r ju gement
Random sequence generation (selection bias)	Unclear risk	"Each patie t ch se a sealed envelope containing the randomized assignment to either ne of the two protocols".
Allocation concealment (selection bias)	Unclear risk	Each p tient chose a sealed envelope containing the randomized assignment to either one of the two protocols".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Do tors and embryolog[ists] were not informed of the study group", unclear if patients blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Doctors and embryolog[ists] were not informed of the study group".
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. No cycle cancellations in the agonist group, and four in the antagonist group (attrition >10%).
Selective reporti g (reporting bias)	Low risk	Trial conducted post-2010. Registration timeline unstated. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted post-2010. Unclear whether it was registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

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Casano 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 412
Participants	**Inclusion criteria:** age <38 years; basal (day 3) FSH <8 U/l; AMH >2 ng/ml and AFC >16; first IVF attempt; predicted high response **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** p edicted hig response **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 205) **Arm 2:** long agonist plus rFSH (n = 20) **Fertilisation method:** IVF or CS **Embryo age at the ime of transfer:** cleavage stage (days 2-4) **Luteal phase su port** vag nal progesterone
Outcomes	**Outcomes re orted** live birth; OHSS; clinical pregnancy; miscarriage; cancellation; oocyte number **Outco es i cluded in the meta-analysis:** live birth; OHSS
Notes	**Type of publication:** published full-text manuscript **Tr l registration:** unstated **Re istration date:** - **Con lict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - werre99@yahoo.com (15 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

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Casano 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computerised algorithm".
Allocation concealment (selection bias)	Low risk	"Sequentially-numbered dark envelopes".
Blinding of participants and personnel (performance bias) All outcomes	High risk	"both the physicians and patients were blinded to the study" but only until just after allocation had been undertaken Subjecti o tcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"both the physicians and patients w re blinded to the study" but only until just after allocation had been undert ken. S bjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly pe formed but possible to extract absolute event numbers from data. Cancellation rates <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial published in 012 but recruitment timeline not stated. Registration status unstated. Selective eporting not detected.
Other bias	Unclear risk	Trial publi hed n 2012 but recruitment timeline not stated. Registration status unsta ed Mult centre study. Effect size difference lower than two-fold between trial arms No other biases detected.

Caserta 2011

Study characteristics

Methods	**Design:** n omised controlled trial **Coun ry:** Ital **Language:** nglish **Se ting:** multicentre **Recru tment period:** 2005 to 2010 **Sample size (total randomised):** 999
Participants	**Inclusion criteria:** age ≤40 years; basal FSH <12 mUI/ml **Exclusion criteria:** >3 previous unsuccessful ART attempts; previous low response to gonadotrophin stimulation defined as <4 preovulatory follicles; history of OHSS; PCOS; abnormal uterine cavity as evaluated by ultrasonography; presence of clinically significant systemic disease **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no

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Caserta 2011 *(Continued)*

	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 501)
	Arm 2: long agonist plus rFSH & rLH (n = 498)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; cancellation; oocyt number; umber of cleavage-stage embryos
	Outcomes included in the meta-analysis: OHSS
Notes	**Type of publication:** published full-text manuscr pt
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: none declared
	Funding: unstated
	Author correspondence: yes - dona ella caserta@uniroma1.it (15 September 2021)
	Calculations used to obtai abso ute eve t numbers: no
	Inclusion in meta-analysis: yes (s nsitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	**Authors' judgem nt**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Random envelope selection."
Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes", unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	H h risk	Open study. Subjective outcomes reported.
Blinding of outcome s-sessment (detection bias) All outcomes	High risk	Open study, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. One hundred and nine patients, in particular 80 in group A and 29 in group B, withdrew before receiving r-hCG and did not complete the study for various reasons. Attrition >10% in group A.

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Caserta 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study conducted up to 2010. Registration status unclear. Selective reporting not detected.
Other bias	Low risk	Trial conducted up to 2010. Multicentre study. Registration timeline unstated. Effect size difference lower than two-fold between trial arms for cancellation rates.

Cattani 2000

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 28
Participants	**Inclusion criteria:** male or tubal infertility **Exclusion criteria:** unstated **Predicted response as stated by h tria sts:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethni ity):** no
Interventions	**Arm** short ntagonist plus rFSH (n = 13) **Arm 2:** long gonist plus rFSH (n = 15) **Fe tilisation method:** unstated **Embryo age at the time of transfer:** unstated **Lute l phase support:** unstated
Outcomes	**Outcomes reported:** amount of gonadotrophin required; serum oestradiol levels; follicle number; oocyte number; mature oocyte number; oocyte atresia rate; pregnancy rate **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated

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Cattani 2000 *(Continued)*

Funding: unstated

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (insufficient data in the abstract to include in the quantitative analysis; no contact details for the authors)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"women were randomised", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only obje tive outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, howe er only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unstated
Selective reporting (reporting bias)	Low risk	S lective reporting not detected.
Other bias	Unclear risk	Study timeline unstated. Trial conducted pre-2000.

Cedrin-Durnerin 2004

Study characteristics

Methods	**D sign:** andomised controlled trial **Cou try:** France **Language:** English **Setting:** multicentre **Recruitment period:** April 2002 to June 2003 **Sample size (total randomised):** 218
Participants	**Inclusion criteria:** age 19–38 years; BMI <30 kg/m^2; normal ovarian function assessed by hormonal determinations on day 3 of a spontaneous cycle Exclusion criteria: previous low (<5 oocytes) or high (>15 oocytes) ovarian response to COS

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Cedrin-Durnerin 2004 *(Continued)*

	Predicted response as stated by the trialists: predicted normal response **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH & rLH (n = 114) **Arm 2:** short antagonist plus rFSH (n = 104) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** unstated **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; miscarriage; ectopic pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** live birth; miscarriage; ectopic pregnancy; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declara ion:** u stated **Funding:** unstated **Author correspondence** none undertaken **Calculations used t btain absolute event numbers:** no **Inclusion i met analysis:** yes (primary analysis - low risk of selection and other biases) **Addit onal comments:** -

Risk of bias

Bias	Au hors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random permutation table".
Allocation concealment (selection bias)	Low risk	"serially numbered, opaque, sealed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, objective and subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding, objective and subjective outcomes reported.

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Cedrin-Durnerin 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute values. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Chakravarty 2000

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** India **Language:** English **Setting:** unstated **Recruitment period:** unstated **Sample size (total randomised):** 381
Participants	**Inclusion criteria:** unstated **Exclusion criteria:** unstated **Predicted response as stated b the trialists:** unstated **Oocyte donors:** no **Cause of inferti ty:** un t ted **Subgro p (a e):** no **Subg oup (BMI):** no **Subgroup (e hnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 123) **A m 2:** l ng agonist plus uFSH (n = 258) **Fert isation method:** IVF or ICSI **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** OHSS; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** conference abstract **Trial registration:** unstated

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Chakravarty 2000 *(Continued)*

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: none undertaken (author contact details not found)

Calculations used to obtain absolute event numbers: yes

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subject e outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"assessor-b nd" tudy.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to obtain absolute event rates f om manuscript, including from percentages (e.g. CPR). Two women had their cyc s cancelled in the uFSH group. Attrition <10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear isk	Trial conducted and published pre-2010. Recruitment timeline not stated. Number of recruiting centres not stated.

Chapon 2021

Study characteris cs

Methods

Design: randomised controlled trial

Country: Brazil

Language: English

Setting: single centre

Recruitment period: January to December 2014

Sample size (total randomised): 168

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Chapon 2021 *(Continued)*

Participants	**Inclusion criteria:** normal FSH <10 mIU/ml; AMH 1-3 ng/ml; AFC >12; and regular menses (25-35 days) **Exclusion criteria:** endocrine pathologies; severe male factor; previous pelvic surgery or ovarian cysts **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 85) **Arm 2:** short antagonist plus hMG (n = 83) **Fertilisation method:** IVF **Embryo age at the time of transfer:** cleavage stage (days 2 4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** clinical pregnancy **Outcomes included in the meta-analysis** o e
Notes	**Type of publication:** published fu -text m nuscript **Trial registration:** NCT0241290 **Registration date:** 9 April 2015 **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calcul tions sed to obtain absolute event numbers:** no **Inclusio i meta-analysis:** no (unclear risk of selection bias, high risk of other biases; primary review outcomes n t reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequen e ge era-tion (selection bias)	Low risk	"computer generated list".
Allocation concealment (selection bias)	Low risk	"randomized cards inside a black envelope with the name of the respective treatment following a computer generated list".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unclear, however only objective outcomes reported.

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Chapon 2021 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"embryologist (…) was blinded to the intervention", however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Retrospectively registered. Selective reporting not detected.
Other bias	High risk	Trial conducted post-2010 and retrospective y registered. Single centre study with plausible recruitment rates. Effect si difference lower than two-fold between trial arms.

Chatillon-Boissier 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** France **Language:** French **Setting:** single centre **Recruitment period:** July 200 to Ju 2009 **Sample size (total randomis d):** 44
Participants	**Inclusion criteria:** low ovarian response diagnosed by one or more of the following: age >38 years and <42 years with serum FSH >9 5 and <12 IU/l; and/or AFC 3-6 on both ovaries in total; and/or previous stimulation failure (4 oocyt s) **Exclusion crite a:** contraindications to COS; AMH <0.2 ng/ml **Predic ed response as stated by the trialists:** predicted low response **Oocyte o ors:** no **Cause of infertility:** various **Su group (age):** no **Su group (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 22) **Arm 2:** agonist flare plus rFSH (n = 22) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated

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Chatillon-Boissier 2012 *(Continued)*

Outcomes	**Outcomes reported:** live birth; clinical pregnancy; cancellation; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - celine.chauleur@chu-st-etien e.f (15 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analy is - includ g all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random seque ce blocks.
Allocation concealment (selection bias)	Unclear risk	Unstate
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open s udy", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open study", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Two women lost to follow-up, and three cancellations (one in the long protocol and two in the short protocol).Attrition rate >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Check 2004

Study characteristics

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Check 2004 *(Continued)*

Methods	**Design:** randomised controlled trial
	Country: United States of America
	Language: English
	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 60
Participants	**Inclusion criteria:** unstated
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & hMG (n = 3)
	Arm 2: short antagonist plus rFSH & hMG (= 30)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reporte :** cl nica pregnancy; cancellation; oocyte number
	Outcomes incl ed in the meta-analysis: none
Notes	**Type f publi ation:** published full-text manuscript
	Trial reg ration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - laurie@ccivf.com (15 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement

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Check 2004 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed b t possible to extract absolute event numbers. Only 19/30 underwen emb yo transfer in the antagonist group, compared to 28/30 in the agonist group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and publi hed pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline un ated.Effect size difference lower than two-fold between trial arms. No other bi ses detected.

Check 2009

Study characteristics	
Methods	**Design:** randomised c trolled trial **Country:** United Sta es of America **Language:** Engl h **Setting:** singl centre **Recruitm nt period:** unstated **Sample size (total randomised):** 70
Participants	**Incl sion criteria:** unstated **Excl sion criteria:** hypogonadotrophic amenorrhoea; diminished ovarian reserve **edicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 35)

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Check 2009 *(Continued)*

	Arm 2: short antagonist plus rFSH & uhCG (n = 35) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; multiple pregnancy; miscarriage; ectopic pregnancy; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - laurie@ccivf.com (15 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analy s - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Suppo t for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low ri k	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low ri k	Unstated, however only objective outcomes reported.
Incomplete out ome d ta (attrition bias) All outcomes	Low risk	One woman from the rFSH group and two women from the hCG group conceived naturally and dropped out (total = 3). Attrition <10% in each group. ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Chen 2004

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** multicentre **Recruitment period:** March 2003 to November 2003 **Sample size (total randomised):** 228
Participants	**Inclusion criteria:** women undergoing COS for ART **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** u stated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n 114) **Arm 2:** long agonist plus uFSH (= 114) **Fertilisation method** I F or ICSI **Embryo age at the ime of t ansfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outc mes reported:** oocyte number; total dose of FSH; duration of stimulation; number of high-quality embryos biochemical pregnancy; OHSS (rates unstated therefore unable to meta-analyse) **Outcomes inc uded in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Tri l registration:** unstated **Reg stration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (insufficient information in the abstract to include in the quantitative analysis; no contact details for the authors)

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Chen 2004 *(Continued)*

Additional comments: -

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open study", subjective outcomes repo ted (e.g., OHSS).
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open study", subjective outcomes eported (e.g., OHSS).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Selective reporti g not detected.
Other bias	Low risk	Multicentr study conducted pre-2010. No other biases identified.

Cheon 2004

Study characteristics	
Methods	**Design:** randomised controlled trial **Count y:** Sou h Korea **Language** English **Setting:** single centre **Rec uitment period:** January to August 2001 **Sample size (total randomised):** 254
Participants	**Inclusion criteria:** age 25-40 years; tubal factor, endometriosis, male factor or unexplained infertility; serum basal FSH <15 mIU/ml; serum basal estradiol <50 pmol/ml; two functional ovaries; normal uterine cavity; <3 previous stimulation cycles; no treatment with gonadotrophins within 1 month before the study **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various

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Cheon 2004 *(Continued)*

	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 131)
	Arm 2: long agonist plus uFSH (n = 123)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: intramuscular progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; cancellat on; oo yte number; number of embryos cryopreserved
	Outcomes included in the meta-analysis: live bi th
Notes	**Type of publication:** published full-text manuscri t
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: none declared
	Funding: unstated
	Author correspondence: yes - kjy omd@samsung.co.kr (15 September 2021)
	Calculations used to obtain abso ute event numbers: yes
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comme ts:

Risk of bias

Bias	Autho s' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear ris	Unstated.
Allocation concealment (selection bias)	Un lear risk	Unstated.
Blinding of particip nts and personnel (p rformance bias) All outcomes	Low isk	"Double blind", only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double blind", only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if ITT analysis strictly performed but possible to extract absolute event numbers. Attrition unclear.

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Cheon 2004 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Cheung 2005

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** single centre **Recruitment period:** April 2001 to December 2003 **Sample size (total randomised):** 66
Participants	**Inclusion criteria:** predicted low response diagnosed by low ovarian response with <4 mature follicles on a long GnRH agonist protocol in their previous IVF cycles, or those with repeated high basal levels of FSH >10 IU/l **Exclusion criteria:** PCOS **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 33) **Arm 2:** long agonist plus rFSH (n = 33) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** hCG
Outcomes	**Outcomes reported:** clinical pregnancy; miscarriage; ongoing pregnancy; ectopic pregnancy; cancellation; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** clinical pregnancy; miscarriage; ongoing pregnancy; ectopic pregnancy; cancellation; oocyte number; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated

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Cheung 2005 *(Continued)*

Registration date: -

Conflict of interest declaration: unstated

Funding: "Serono HK provided samples of Cetrorelix."

Author correspondence: yes - lpcheung@cuhk.edu.hk (15 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated rand m nu bers.
Allocation concealment (selection bias)	Low risk	Opaque envelopes used (SNOSE), a d the following has been confirmed by the study authors via email on 23/09/2021: "A research nurse not involved in the clinical care of the patient coordinated the randomization process and distribution of medications t roughout the treatment cycles."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, doctor and embryologists blinded, as confirmed by the trial authors on 23/09/2021 v email. Subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	I T analysis not performed. High cancellation rates in both groups (38.7% in the ntagonist group, 34.4% in the agonist group).
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Cota 2012

Study characteris ic

Methods

Design: randomised controlled trial

Country: Brazil

Language: English

Setting: single centre

Recruitment period: May 2011 to October 2011

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Cota 2012 *(Continued)*

	Sample size (total randomised): 64
Participants	**Inclusion criteria:** age ≤37 years; first IVF/ICSI cycle; BMI <30 kg/m^2; regular menses, and both ovaries present **Exclusion criteria:** PCOS; severe endometriosis; ovarian cysts diagnosed on transvaginal ultrasound; basal FSH ≥10 IU/ml **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 32) **Arm 2:** short antagonist plus rFSH & rLH (n = 32) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** unst t d **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** cancellation oo yte umber **Outcomes included in the met analysis:** cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** 011/11 Women's Health Reference Centre **Registration date:** ns ated **Conflict of inte st declaration:** none declared **Fundi g:** uns ated **Author c r espondence:** yes - joaobatista@crh.com.br (16 September 2021) **Calculations used to obtain absolute event numbers:** no **In usion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Ad itional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated table".
Allocation concealment (selection bias)	Low risk	Nurse blinded to subject identities performed all the lot draws.

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Cota 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding of participants or personnel as confirmed by Joao Batista via email (20/09/2021), however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of participants or personnel as confirmed by Joao Batista via email (20/09/2021), however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up or cancelled cycles as confirmed by the authors via email (20/09/2021).
Selective reporting (reporting bias)	Low risk	Trial published post-2010. Registration status unclea Selective reporting not detected.
Other bias	Low risk	Trial published post-2010 Not registered internationally but registered prospectively locally (Project refere ce 011/11, Women's Health Reference Centre, registered on 27/04/201 as confirmed by the trial authors (20/09/2021). Single centr study wi h plausible recruitment rates. Effect size difference lower than two-fold etween trial arms.

Cruz 2017

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** multicentr **Recruitment pe iod:** un tated **Sample size otal r ndomised):** 208
Participants	**Inclusi n c iteria:** age 18-35 years; weight <60 kg; regular menstrual cycles; no hereditary or chromosomal disea es; normal karyotype; negative for sexually transmitted infections; antral follicle count per ovary ≥6 **Ex lusion criteria:** PCOS; multifollicular ovaries **Pr dicted response as stated by the trialists:** predicted normal response **Oocyte donors:** yes **Cause of infertility:** N/A **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 137) - two arms merged (see additional comments) **Arm 2:** short antagonist plus hMG (n = 71)

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Cruz 2017 *(Continued)*

	Fertilisation method: N/A **Embryo age at the time of transfer:** N/A **Luteal phase support:** N/A
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT02213627 **Registration date:** 11 August 2014 **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - antonio.requena@ivi.es (23 February 2022) **Calculations used to obtain absolute event numb rs:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias, high risk of other biases; primary review outcomes not reported) **Additional comments:** A total of 208 oocyt dono s undergoing a short antagonist protocol were allocated to COS with corifollitropin alpha (n = 68) daily rFSH (n = 69) or HP-hMG (n = 71). For the purposes of meta-analysis, we planned to merg the the corifollitropin alpha and rFSH groups.

Risk of bias

Bias	Authors' judgement	Support for udgement
Random sequence generation (selection bias)	Low risk	"Rando ization was performed with an online randomization programme [leatorMetod; Ramos Alvarez]".
Allocation concealment (selection bias)	Unclear risk	Un tated.
Blinding of participants and personnel (performance bias) All outcomes	Low ri k	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Lo risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly reported. Nine women allocated to the corifollitropin alpha group did not receive the intervention; six did not receive the intervention in the rFSH group; and 11 in the HP-hMG group. Attrition rate >10% in all groups.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	High risk	Multicentre study, prospectively registered (NCT02213627). The original target sample size was 300 participants as stated in the trial registration record, however only 208 women were recruited.

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Davar 2010

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** November 2007 to November 2008 **Sample size (total randomised):** 94
Participants	**Inclusion criteria:** at least one previous failed IVF cycle in which <4 follicles with a mean diameter of 16 mm were achieved and/or serum oestradiol levels asured on the day of hCG administration were ≤500 pg/ml **Exclusion criteria:** day 3 serum FSH ≥12 mIU/ml **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus rFSH & MG (n = 49) **Arm 2:** short antagonist plus letrozole & rFSH & hMG (n = 45) **Fertilisation method:** IVF o ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Lutea phase support:** intramuscular progesterone
Outcomes	**Outcomes ported:** clinical pregnancy; cancellation; oocyte number **O tcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Tria registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - homaoskouian@gmail.com (16 September 2021) **Calculations used to obtain absolute event numbers:** yes **Inclusion in meta-analysis:** no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported)

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Davar 2010 *(Continued)*

Additional comments: -

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective out omes rep rted.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Six women were cancelled in the flare group, and ten in the antagonist group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2 10. Selective reporting not detected.
Other bias	Low risk	Trial cond ted p e-2010. Single centre study with plausible recruitment rates. No conc rns regarding validity of results. Effect size difference lower than two-fold etwee trial arms. No other biases detected.

Davar 2013

Study characteristics	
Methods	**Design:** rand mised controlled trial **Country:** I n **La guage:** English **Setti g:** single centre **Rec itment period:** March 2011 to March 2012 **mple size (total randomised):** 116
Participants	**Inclusion criteria:** low ovarian response in previous cycle; anticipated low response **Exclusion criteria:** stage III-IV endometriosis; autoimmune or chromosomal disorders; endocrine or metabolic diseases; existence of only one ovary; day 3 FSH >15 mIU/ml; severe male factor; hydrosalpinx **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various

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Davar 2013 *(Continued)*

	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 58)
	Arm 2: agonist flare plus rFSH (n = 58)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: various
	Luteal phase support: intramuscular progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; miscarriage; cance ation; oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manusc pt
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: none de ared
	Funding: unstated
	Author correspondence: none undertaken
	Calculations used to obtain absolu event numbers: no
	Inclusion in meta-analysis: no (uncl ar risk of selection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors jud emen	Support for judgement
Random sequence generation (selection bias)	Low ris	"Randomized assignment of the two treatments was performed by a computer-based program."
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Single blind trial", subjective outcomes reported (e.g. cancellation).
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Single blind trial", subjective outcomes reported (e.g. cancellation).
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.

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Davar 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	Study conducted post-2010, registration status unstated. Single centre study with plausible recruitment rates.

Davar 2018

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** October 2016 to December 20 6 **Sample size (total randomised):** 120
Participants	**Inclusion criteria:** low ovarian response (o gna criteria) **Exclusion criteria:** age <18 or >42 years; BMI ≥ 0 kg/m^2; endocrine or metabolic disorders; severe endometriosis; severe male factor (patien with azoospermia and frozen-thawed semen) **Predicted response as sta ed by h tria sts:** predicted low response **Oocyte donors:** no **Cause of infertility:** low varian reserve **Subgroup (age):** no **Subgroup (BMI):** yes 30 kg/m^2) **Subgrou (thnic ty):** no
Interventions	**Arm** short antagonist plus rFSH (n = 58) **Arm 2:** agon t flare plus rFSH (n = 62) **Fe tilisation method:** IVF or ICSI **Embry age at the time of transfer:** cleavage stage (days 2-4) **Lute l phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; ongoing pregnancy; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** IRCT2016071628950N1 **Registration date:** 20 October 2016 **Conflict of interest declaration:** none declared

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Davar 2018 *(Continued)*

Funding: "This study was supported by Yazd Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran."

Author correspondence: yes - nosrat20@yahoo.com (16 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random digit software".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Physicians performing the follicular aspiration were blinded, but no statement made on participant linding. Subjective outcomes performed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT a alysis not strictly performed but possible to extract absolute event numbers. E ght women cancelled in the antagonist group, and twelve women cancelled in he agonist group. Attrition >10%.
Selective reporting (reporting bias)	Low risk	Tria conducted post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Daya 1995

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Canada **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 232
Participants	**Inclusion criteria:** women undergoing COS for ART

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Daya 1995 *(Continued)*

	Exclusion criteria: age >38 years; first ART cycle; day 3 FSH concentration >15 IU/l; total motile sperm count <5x10^6 in the male
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** agonist flare plus uFSH (n = 115)
	Arm 2: agonist flare plus hMG (n = 117)
	Fertilisation method: unstated
	Embryo age at the time of transfer: cleavage st ge (days 2-4
	Luteal phase support: hCG or progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; ongoi g pregnancy; miscarriage; oocyte number
	Outcomes included in the meta-analysis: one
Notes	**Type of publication:** published full tex manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest decl ration unstated
	Funding: unstated
	Author correspondence: none undertaken (author contact details not found)
	Calculatio s use to obtain absolute event numbers: no
	Inclu on in meta-analysis: no (unclear risk of other biases; primary review outcomes not reported)
	Additiona comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera tion (selection bias)	Low isk	Random number table.
Allocation concealm nt (selection bias)	Low risk	Sealed opaque discs centrally managed.
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Patients and physicians blinded to the intervention.

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Daya 1995 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients and physicians blinded to the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Nine women were cancelled in the uFSH group, and six were cancelled in the hMG group. Attrition <10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Recruitment rates clear as study timeline unstated. Effect size difference lower than two-f ld betwee trial arms. No other biases detected.

Decleer 2020

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Belgium **Language:** English **Setting:** single centre **Recruitment period:** Novemb r 201 t December 2015 **Sample size (total randomis d):** 105
Participants	**Inclusion criteria:** age <40 years; ≤3 previous IVF attempts; absence of major endocrinological disorders **Exclusion criteria:** PCOS **Predicte r spons as stated by the trialists:** unstated **Oocy e dono s:** no **Cause of in rtility:** various **Subgroup (age):** no **Subg up (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH & uhCG (n = 50) **Arm 2:** short antagonist plus rFSH & hMG (n = 55) **Fertilisation method:** unstated **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; ongoing pregnancy; oocyte number

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Decleer 2020 *(Continued)*

	Outcomes included in the meta-analysis: live birth; clinical pregnancy; ongoing pregnancy; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** Eudract 2012-005676-34 **Registration date:** 14 December 2012 **Conflict of interest declaration:** unstated **Funding:** none sought **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk f selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer randomisation".
Allocation concealment (selection bias)	Low risk	Independent tudy coordinator.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open tr l however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Ope trial, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low ri k	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Demirol 2005

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Turkey

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Demirol 2005 *(Continued)*

	Language: English
	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 106
Participants	**Inclusion criteria:** low response defined as having at least two negative cycles with one of the following criteria: (1) three oocytes retrieved; (2) three follicles of 16 mm on hCG day; and (3) maximal serum oestradiol <500 pg/ml
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: predicted low resp nse
	Oocyte donors: no
	Cause of infertility: low ovarian response
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH & rLH (n 53)
	Arm 2: short antagonist plus rFSH (n = 53)
	Fertilisation method: unstated
	Embryo age at the time of transfe unstated
	Luteal phase support: unsta d
Outcomes	**Outcomes reported:** stimulation parameters; fertilisation rate; implantation rate; pregnancy rate; duration of stimulation; ooc te number; embryo number
	Outcomes included the meta-analysis: none
Notes	**Type of ub catio** conference abstract
	Trial egistr tion: unstated
	Registratio date: -
	Conflict of interest declaration: unstated
	Fundi g: unstated
	Author correspondence: none undertaken (author contact details not found)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (insufficient data in the abstract for quantitative analysis; no contact details for the authors found)
	Additional comments: -

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Demirol 2005 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"patients were prospectively randomised", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective out omes port d.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis was p formed.
Selective reporting (reporting bias)	Low risk	No selective reporting det cted.
Other bias	Unclear risk	Study timeline unstated. Other biases unclear.

Demirol 2009

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Turkey **Language:** English **Setting:** single ntre **Recrui ment eriod:** unstated **Sample iz (total randomised):** 90
Participants	**Inclusion criteria:** three criteria for low ovarian response, including baseline (day 3) FSH >15 mIU/ml <4 oocytes in all previous IVF attempts and a minimum of two previous IVF cycles with low ovarian r sponse (oestradiol concentration on the day of hCG injection <500 pg/ml or <4 mature oocytes retr ved **Exclusion criteria:** BMI >26 kg/m^2; PCOS; stage III–IV endometriosis (revised American Fertility Society classification, 1985); inflammatory, autoimmune, or chromosomal disorders; endocrine or metabolic disease, including hyperprolactinaemia; only one ovary; infertility medications (clomifene citrate and/or gonadotrophins) within the past month **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no

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Demirol 2009 *(Continued)*

	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** agonist flare plus hMG (n = 45)
	Arm 2: short antagonist plus hMG (n = 45)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: none declar d
	Funding: unstated
	Author correspondence: yes - ademirol@gma l.com (16 September 2021)
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: no (uncl isk of other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgemen	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation".
Allocation concealment (selection bias)	Low risk	Sealed envelopes managed by a specialist nurse.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outc me as sessment (detect n b as) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Three cycles cancelled in the agonist group, and five in the antagonist group. Attrition >10% in the antagonist group.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Demirol 2009 *(Continued)*

Other bias	Unclear risk	Trial conducted pre-2010. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Depalo 2009

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** November 2004 to Decemb r 2007 **Sample size (total randomised):** 136
Participants	**Inclusion criteria:** age 24-42 years; baseline FSH level <10 IU/ml; absence of uterine or ovarian abnormalities or severe endometriosis or PCOS; ≤3 p evious IVF attempts; no oral contraceptive pills taken before the stimulation cycle **Exclusion criteria:** unstated **Predicted response as stated by he t ialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethn city):**
Interventions	**Arm 1:** hort antagon t plus rFSH (n = 67) **Arm 2:** ong agonist plus rFSH (n = 69) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **L teal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; ongoing pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated

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Depalo 2009 *(Continued)*

Author correspondence: yes - milalorusso@yahoo.it (16 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective ou omes repo ed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Embryologists bli ded, but no mention of blinding of other personnel.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analy s not st ictly performed but possible to extract absolute event numbers. Six w men cancelled in the antagonist group and another 3 excluded from an lysis (total = 9). Six women were excluded from the agonist group's analysis. Att ition rate >10% in the agonist arm.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

De Placido 2001

Study characteristics

Methods	**Desi n:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** November 1999 to July 2000 **Sample size (total randomised):** 43
Participants	**Inclusion criteria:** previous low initial response to recombinant FSH **Exclusion criteria:** unstated

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De Placido 2001 *(Continued)*

	Predicted response as stated by the trialists: predicted low response
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & hMG (n = 20)
	Arm 2: long agonist plus rFSH (n = 23)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: intramuscular progesterone
Outcomes	**Outcomes reported:** miscarriage; oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text m n script
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaratio : uns t d
	Funding: unstated
	Author correspondence: yes c viggi@hotmail.com (16 September 2021)
	Calculations used t obtain absolute event numbers: no
	Inclusion in meta-analy is: no (unclear risk of selection bias [allocation concealment unstated]; primary review outc mes not reported)
	Addit onal comments: -

Risk of bias

Bias	Au hors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.

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De Placido 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detec ed.

De Placido 2005

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** multicentre **Recruitment period:** February to December 2003 **Sample size (total randomised):** 130
Participants	**Inclusion criteria:** age 18–37 years; mens rual cycles 24-35 days; basal FSH (day 3 of a spontaneous menstrual cycle) concentrations ≤9 IU/l; hysteroscopic evidence of a normal uterine cavity within the last 6 months; inadequate response **Exclusion criteria:** BMI <18.0 and >28.0 kg/m^2; PCOS; stage III–IV endometriosis; chromosomal abnormalities, endocrinologica and/or autoimmune disorders; >2 previously unsuccessful IVF or ICSI cycles; and presence of on one ovary **Predicted response as stated by the trialists:** predicted low response **Oocyte dono s:** no **Cause f in ertility:** various **Subgroup (ag :** no **S bgroup (BMI):** yes (<30 kg/m^2) **Su group (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 65) **Arm 2:** long agonist plus rFSH (n = 65) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** unstated **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** ongoing pregnancy; miscarriage; cancellation; oocyte number

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De Placido 2005 *(Continued)*

	Outcomes included in the meta-analysis: ongoing pregnancy; miscarriage; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** "This study was realised with grants from the Ministero dell'Ist uzione, dell'Universita` e della Ricerca (PRIN annualita` 2003 prot. 2003065093_002)." **Author correspondence:** yes - alviggi@unina.it (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgem nt
Random sequence generation (selection bias)	Low risk	Computer-generat d ra om number tables.
Allocation concealment (selection bias)	Low risk	Adequate per ormed via a central telephone number, as per Van Wely 2011.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unst ted, s bjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded assessors.
Incomplete outcome data (attrition bias) All outcomes	High sk	ITT analysis not strictly performed but possible to extract absolute event numbers. Six women were cancelled in the rLH group and seven were cancelled in the rFSH group. Attrition >10% in the rFSH-only group.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low isk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

De Placido 2006

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Italy

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De Placido 2006 *(Continued)*

	Language: English
	Setting: single centre
	Recruitment period: July 2002 to February 2004
	Sample size (total randomised): 133
Participants	**Inclusion criteria:** age ≥37 years or day 2 FSH (basal FSH) serum concentration <9 IU/l; menstrual cycles ranging between 24–35 days; hysteroscopic evidence of a normal uterine cavity; ICSI
	Exclusion criteria: BMI <18.0 and >28.0 kg/m^2; PCOS; stage III–IV endom triosis; chromosomal abnormalities, endocrinological and/or autoimmune disorders; >2 previously unsuccessful IVF or ICSI cycles; and presence of only one ovary
	Predicted response as stated by the trialists: predicted low sponse
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH & rLH (n = 66)
	Arm 2: agonist flare plus rFSH & rLH (n 67)
	Fertilisation method: ICSI
	Embryo age at the time of transf r: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** ongoing pregnancy; cancellation; oocyte number
	Outcomes inclu ed i the meta-analysis: none
Notes	**Type of publ cation** published full-text manuscript
	Trial gistr tion: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: "This study was supported by grants from the Ministero dell'Istruzione, dell'Università e della Rice ca (PRIN annualitá 2004 prot. 2004061475_003)."
	Author correspondence: yes - alviggi@unina.it (16 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement

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De Placido 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Computer-generated list".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Four patien s in the antagonist group and five women in the agonist group had th ir cy les cancelled because of an inadequate ovarian response. Attrition <10% in both rial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and publi hed pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns rega d g validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

De Sutter 1999

Study characteristics	
Methods	**Design:** randomised c trolled trial **Country:** Belgium **Language:** Engl h **Setting:** mult centre **Recruitm nt period:** unstated **Sample size (total randomised):** 496
Participants	**Incl sion criteria:** age 18-38 years **Excl sion criteria:** unstated **edicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 232)

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De Sutter 1999 *(Continued)*

	Arm 2: long agonist plus uFSH (n = 231) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number; embryo number; pregnancy rate; OHSS (moderate/severe); gonadotrophin dose; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (insufficien data the abstract to include in the quantitative analysis; no up-to-date contact details for the authors) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Suppo t for judgement
Random sequence generation (selection bias)	Unclear risk	women were randomised", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High r k	"Assessor-blind", subjective outcomes (e.g., OHSS) reported.
Blinding of outcome assessment (detection bias) All outcomes	Low ri k	"Assessor-blind", subjective outcomes (e.g., OHSS) reported.
Incomplete out ome d ta (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Multicentre study conducted pre-2010. No evidence of other biases detected.

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Devesa 2010

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 221
Participants	**Inclusion criteria:** age <45 years; at least one of the following: prio cycle cancellation (follicular development<4 follicles after 8–10 days of intensive gonadotrop n stimulation), prior low response to COS (<5 follicles larger than 12 mm of diameter on the day f hCG administration after intensive stimulation); FSH day 3 + FSH day 10 ≥25) and/or AFC <7 f llicles **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus rFSH (n = 38) **Arm 2:** short antagonist plus rFSH (n = 51) **Arm 3:** agonist flare plus rFSH & hMG (n = 42) **Arm 4:** short antagonist plus rFSH & hMG (n = 41) **Fertil sation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Lut al phase support:** vaginal progesterone
Outcomes	**Outc mes reported:** cancellation; oocyte number **Out omes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no

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Devesa 2010 *(Continued)*

Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated randomisation list in a 1:1 ratio".
Allocation concealment (selection bias)	Unclear risk	"Study nurse coordinator".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not perfor ed
Selective reporting (reporting bias)	Low risk	Selective eporting not detected.
Other bias	Unclear risk	Unstat d.

Devroey 1995

Study characteristics

Methods	**Design** ran omised controlled trial **Country:** Belg m **La guage:** English **S tting** single centre **Recruitment period:** January 1990 to October 1992 **Sample size (total randomised):** 158
Participants	**Inclusion criteria:** age 18-37 years; menstrual cycle ranging from 27 ± 3 to 32 ± 3 days **Exclusion criteria:** endocrine anomalies; PCOS; recurrent corpus luteum insufficiency and absence of ovarian function; male infertility; contraindications to gonadotrophin treatment; extensive adhesions; ovarian anomalies; hypertension; chronic cardiovascular, hepatic, renal or pulmonary disease; current or previous abuse of alcohol or drugs; alcohol or drugs; use of gonadotrophin treatment within the 3 months preceding participation in the study **Predicted response as stated by the trialists:** unstated

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Devroey 1995 *(Continued)*

	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** hMG without pituitary suppression (n = 93)
	Arm 2: uFSH without pituitary suppression (n = 65)
	Fertilisation method: unstated
	Embryo age at the time of transfer: unstated
	Luteal phase support: hCG
Outcomes	**Outcomes reported:** clinical pregnancy; ongoing pregnancy; cancellation
	Outcomes included in the meta-analysis: clinical pregnan y; ongoing pregnancy; cancellation
Notes	**Type of publication:** published full-text man script
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: nstated
	Funding: "This project was supported by grants from the Belgian Fund for Medical Research."
	Author correspondence: non unde taken
	Calculations used to obtain abs lute event numbers: no
	Inclusion in meta-analysis yes (primary analysis - low risk of selection and other biases)
	Additional comments:

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list.
Allocation concealment (selection bias)	Lo risk	"Drug assignment list only available to the study coordinator"
Blinding of parti ipants and personnel (pe fo mance bias) All outcomes	High risk	Open study, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor-blind study.
Incomplete outcome data (attrition bias)	Low risk	ITT analysis performed. Five women cancelled in the hMG group and three in the uFSH group. Attrition <10% in both trial arms.

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Devroey 1995 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Devroey 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** International (Belgium, Czech Republic Denmark, Poland, Spain, Sweden and Turkey) **Language:** English **Setting:** multicentre **Recruitment period:** September 2009 to November 2011 **Sample size (total randomised):** 749
Participants	**Inclusion criteria:** age 21–34 years; BM 18–25 kg/m^2; unexplained infertility or mild male factor; eligible for ICSI according to the inve tigator; <12 months' infertility before randomisation; regular menstrual cycles (24–35 days), p esumed to be ovulatory; hysterosalpingography, hysteroscopy, or transvaginal ultrasound documenting a uterus consistent with expected normal function; transvaginal ultrasound documenting presence and adequate visualisation of both ovaries without evidence of abnormality; the trial cycle being the first or second COS cycle ever or the first or second COS cycle after having achieved ongoing pregnan y a previous COS cycle; early follicular phase serum levels of FSH of 1–12 IU/l; and early folli ula phase total AFC (diameter 2–10 mm) >10 for both ovaries combined. **Exclusion criteria:** PCOS; endometriosis; low response in previous COS cycle; previous severe OHSS; recurrent miscar iage; c rent or past abuse of alcohol or drugs; smoking (>10 cigarettes/day) **Predict d re ponse s stated by the trialists:** unstated **Oocyt don rs:** no **Cause of infe tility:** various **Subgroup (age):** yes (<35 years) **bgro p (BMI):** yes (<30 kg/m^2) **Sub roup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus hMG (n = 374) **Arm 2:** short antagonist plus rFSH (n = 375) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** blastocyst (day 5+) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; OHSS; clinical pregnancy; ongoing pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number; cleavage embryo number; blastocyst number

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Devroey 2012 *(Continued)*

	Outcomes included in the meta-analysis: live birth; OHSS; clinical pregnancy; ongoing pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number; cleavage embryo number; blastocyst number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT00884221 **Registration date:** 20 April 2009 **Conflict of interest declaration:** "P.D., A.P., and A.N.A. received fees from Ferring Pharmaceuticals to cover their institutions' work during the clinical trial reported in this m nuscript. P.D. has received consultancy fees and grants from Ferring Pharmaceuticals, MSD, Merck Serono, and IBSA. A.P. has received consultancy fees from Ferring Pharmaceuticals. A.N.A. has received consultancy fees from Ferring Pharmaceuticals and has been on the speakers bureau for Ferrin Pharmaceuticals, MSD, and Merck Serono. J.-C.A. is an employee of Ferring Pharmaceuticals **Funding:** "The clinical trial was sponsored by Ferring Pharma euticals." **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Rand miza was performed with the use of a computer-generated random zation list stratified by center."
Allocation concealment (selection bias)	Low risk	ha dled by a study nurse to maintain blinding of the investigators".
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open label trial", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The trial was assessor blinded, and all investigators, central assessors, laboratory personnel, and sponsor staff involved in analyzing and interpreting data were kept blinded to the treatment allocation throughout the trial."
Incomplete outcome data (attrition bias) All outcomes	Low r sk	ITT analysis performed. Attrition <10% in both trial arms.
Selective report ng (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Multicentre study. Effect size difference lower than two-fold between trial arms.

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Dickey 2001

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 177
Participants	**Inclusion criteria:** age 18-39 years; regular ovulatory cycles **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** un tated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus uFSH (n = 119) - two arms merged (see additional comments) **Arm 2:** long agonist plus rFSH (n 58) **Fertilisation method:** IVF **Embryo age at the tim of transfer:** unstated **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes repor ed:** oocyte number; peak serum oestradiol level; biochemical pregnancy; clinical pregna cy; ongoing pregnancy; adverse events; ectopic pregnancy **Outco es i cluded in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Tr l registration:** unstated **Re istration date:** - **Con lict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (insufficient data in the abstract to include in the quantitative analysis; no contact details for the authors found)

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Dickey 2001 *(Continued)*

Additional comments: participants were randomised to undergo a long GnRH agonist protocol using uFSH SC (n = 60), uFSH IM (n = 59) or rFSH SC (n = 58). For the purposes of meta-analysis, we planned to amalgamate the two uFSH groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open label", subjective outcomes r por d (e.g., adverse events).
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open label", subjective outcomes reported (e.g., adverse events).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Selective epo tin not detected.
Other bias	Low risk	Mult entre tudy conducted pre-2010. No other biases detected.

Dickey 2003

Study characteristics

Methods	**Design:** rand mised controlled trial **Country:** U ited States of America **La guage:** English **Setti g:** single centre **Rec itment period:** unstated **mple size (total randomised):** 80
Participants	**Inclusion criteria:** age ≤38 years; baseline FSH ≤10 IU/l; baseline AFC >5; BMI >19 and <32 kg/m^2; regular cycles >26 and <34 days; ≤1 previous ART cycle **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated

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Dickey 2003 *(Continued)*

	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 39)
	Arm 2: long agonist plus rFSH (n = 41)
	Fertilisation method: unstated
	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; durat on of s imulation; dose of gonadotrophins; oocyte number; embryo number; ongoing pre nancy
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** conference abstract
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none unde take
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: no insufficient data in the abstract; no author contact details found)
	Additional comments: -

Risk of bias

Bias	Authors jud emen	Support for judgement
Random sequence generation (selection bias)	Unclea risk	"randomised", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unc ar risk	Unstated, subjective outcomes reported (e.g., OHSS).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., OHSS).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed. Attrition per arm unclear.

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Dickey 2003 *(Continued)*

Selective reporting (reporting bias)	Low risk	No selective reporting detected.
Other bias	Low risk	Multicentre study conducted pre-2010. No evidence of other biases identified.

Dickey 2003a

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 238
Participants	**Inclusion criteria:** age 18-39 years; BMI ≤34 kg/m^2; non-smoking, premenopausal females; regular ovulatory menstrual cycles (24–35 days); unremarkable medical history and physical examination with normal baseline haematology and clinical chemistry; normal range serum oestradiol, FSH, LH, testosterone, dehydroepiandrosterone sulphate, prolactin and TSH; seronegativity for hepatitis B and C, HIV and syphilis; negative pregnancy test before starting treatment; normal SFA (WHO criteria) within 6 months of study entry **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility** various **Subgroup (age)** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus uFSH (n = 120) **Arm 2:** long agonist plus rFSH (n = 118) **Fertilisation method:** IVF **Embryo age at the time of transfer:** unstated **Luteal phase support:** IM or PV progesterone
Outcomes	**Outcomes reported:** live birth; OHSS; clinical pregnancy; ongoing pregnancy; oocyte number **Outcomes included in the meta-analysis:** live birth; OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** -

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Dickey 2003a *(Continued)*

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: yes - renee@fertilityinstitute.com (16 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open-label" trial, su jective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open-label" tr al subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT an lysis not strictly performed but possible to extract absolute event numbe s Only 113 women underwent oocyte retrieval in the uFSH group and 115 in the rFSH group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Tria s conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trials conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

DiLuigi 2011

Study characteristi s

Methods

Design: randomised controlled trial

Country: United States of America

Language: English

Setting: single centre

Recruitment period: July 2006 to July 2009

Sample size (total randomised): 54

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DiLuigi 2011 *(Continued)*

Participants	**Inclusion criteria:** age 21–44 years; low response in prior IVF cycle (at least one of the following: <4 mature follicles, <4 oocytes retrieved, peak oestradiol <1,000 pg/ml, prior IVF cycle cancelled for low response); or predicted low response (at least one of the following: age >40 years, FSH >10 mIU/ml, low response in prior gonadotrophin stimulation cycle [oestradiol <500 pg/ml]) **Exclusion criteria**: previous ART treatment with GnRH antagonist or microdose long agonist protocol **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus hMG & rFSH (n = 26) **Arm 2:** agonist flare plus hMG & rFSH (n = 28) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage s age (days 2-4) **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** live birth; clinical regnancy; ongoing pregnancy; cancellation; oocyte number **Outcomes included in the meta-a lysis** live birth
Notes	**Type of publication:** published full-t xt manuscript **Trial registration:** unstated **Registration date:** **Conflict of interest de l ation:** "A.J.D. has nothing to disclose. L.E. has nothing to disclose. D.W.S. has nothing to di close. C.A.B. is a member of Merck speaker's bureau. J.C.N. is a member of EMD Serono peak r's bur au." **Fundi g:** unstated **Author corres ondence:** yes - diluigi@uchc.edu (16 September 2021) **Ca culations used to obtain absolute event numbers:** no **I clusi n in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outc mes [live birth and/or OHSS]) **dditional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomization in a 1:1 ratio".
Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes were used for protocol assignment", however unclear if SNOSE.

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DiLuigi 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Six women were cance led in the LPG group and nine in the ML group. Attrition >10% in both trial arms
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010 Sele tive re orting not detected.
Other bias	Low risk	Trial conducted pre-2010 S ngle entre tudy with plausible recruitment rates. No concerns regarding v lidity of re ults. Effect size difference lower than two-fold between trial arms. o other bia es detected.

Dirnfeld 1991

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Israel **Language:** English **Setting:** single centre **Recruitment perio :** un tated **Sample size (to al randomised):** 54
Participants	**Inclusi n cri ria:** a least one previous cycle cancellation due to inadequate response; normal early follic lar pha e prolactin, FSH, LH, testosterone and thyroid function **Exclusion riteria:** unstated **Pr dicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cau e of infertility:** low ovarian reserve **bgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 28) **Arm 2:** agonist flare plus hMG (n = 26) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated

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Dirnfeld 1991 *(Continued)*

	Luteal phase support: intramuscular progesterone
Outcomes	**Outcomes reported:** cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact etails ot found) **Calculations used to obtain absolute event numbe** no **Inclusion in meta-analysis:** no (unclear risk of se ection bias [allocation concealment unstated]; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgem nt
Random sequence generation (selection bias)	Low risk	"Random num ers table".
Allocation concealment (selection bias)	Unclear risk	Uns ated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclea risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis possible to undertake based on absolute event numbers. Two cycles in the long agonist group were cancelled, and ten in the short flare protocol (total = 12). Attrition rate >10%.
Selective reporting (reporting bias)	Low isk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Drakakis 2002

Study characteristics

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Drakakis 2002 *(Continued)*

Methods	**Design:** randomised controlled trial
	Country: Greece
	Language: English
	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 99
Participants	**Inclusion criteria:** unstated
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 46)
	Arm 2: long agonist plus hMG & uFSH (= 53)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: hCG
Outcomes	**Outcomes reporte :** cancel ation; oocyte number
	Outcomes incl ed in the meta-analysis: none
Notes	**Type f publi ation:** published full-text manuscript
	Trial reg ration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none undertaken (author contact details not found)
	Calculations used to obtain absolute event numbers: yes
	Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement

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Drakakis 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"randomized prospectively", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed b t possible to extract absolute event numbers. Attrition rate <10% in both rial arms
Selective reporting (reporting bias)	Low risk	Trial conducted and publi hed pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline un ated. Effect size difference lower than two-fold between trial arms. No other bi ses detected.

Drakakis 2002a

Study characteristics	
Methods	**Design:** randomised c trolled trial **Country:** Greece **Language:** Engl h **Setting:** singl centre **Recruitm nt period:** unstated **Sample size (total randomised):** 70
Participants	**Incl sion criteria:** age <39 years; normal serum gonadotrophin levels; normal basal hormone profiles **Excl sion criteria:** unstated **edicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 36)

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Drakakis 2002a *(Continued)*

	Arm 2: long agonist plus hMG (n = 34)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** cancellation; oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none undertaken (autho contact details not found)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of s lection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support fo judgement
Random sequence generation (selection bias)	Unclear risk	"rand mly divided".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	U lear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT performed. Five women were cancelled in the hMG group. Attrition >10% in the hMG trial arm.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Drakakis 2005

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Greece **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 46
Participants	**Inclusion criteria:** normal serum gonadotrophin levels **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** p edicted no mal response **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n 22) **Arm 2:** long agonist plus rFSH & hMG (n = 24) **Fertilisation method** u stated **Embryo age at the ime of t ansfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outc mes reported:** clinical pregnancy; oocyte number **Outcomes ncluded in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial gistration:** unstated **Regi tration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - pdrakakis@hol.gr (16 September 2021) **Calculations used to obtain absolute event numbers:** yes **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

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Drakakis 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"prospective randomization by closed envelopes".
Allocation concealment (selection bias)	Unclear risk	"prospective randomization by closed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes repo ted.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective o comes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly pe formed but possible to extract absolute event numbers from percentages. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted a d publ shed pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study tim lin uns ated. Effect size difference lower than two-fold between trial arms No the biases detected.

Drakakis 2009

Study characteristics

Methods	**Design:** n omised controlled trial **Coun ry:** Greece **Language:** nglish **Se ting:** single centre **Recru tment period:** January 2007 to December 2007 **Sample size (total randomised):** 120
Participants	**Inclusion criteria:** age 36-42 years; BMI ≤32 kg/m^2; regular menstrual cycles (21-35 days), normal serum FSH, prolactin and TSH; normal uterine cavity confirmed by hysteroscopy or hysterosalpingography; no treatment with clomifene citrate or gonadotrophins for at least 3 months before screening **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various

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Drakakis 2009 *(Continued)*

	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** agonist flare plus rFSH & uhCG (n = 60)
	Arm 2: agonist flare plus rFSH & rLH (n = 60)
	Fertilisation method: unstated
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** moderate OHSS; clinical pregnancy
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manusc pt
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: none de ared
	Funding: unstated
	Author correspondence: yes - pd akak s@hotmail.com; loutradis@otenet.gr (15 September 2021)
	Calculations used to obtain absolu event numbers: no
	Inclusion in meta-analysis: no (uncl ar risk of selection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors jud emen	Support for judgement
Random sequence generation (selection bias)	Low ris	Computer randomisation.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unc ar risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis possible to undertake based on absolute numbers. Six cycles were cancelled (two in the hCG group, and 4 in the LH group). Attrition <10% in both trial arms.

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Drakakis 2009 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Drakopoulos 2017

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** International (Belgium and Vietnam) **Language:** English **Setting:** multicentre **Recruitment period:** March 2013 to May 2016 **Sample size (total randomised):** 152
Participants	**Inclusion criteria:** age <40 years old, fulfilling the Bologna criteria for low ovarian response **Exclusion criteria:** uterine abnormalities; recent history of any current untreated endocrine abnormality; unilateral or bilateral hydrosalpinx (visible on ultrasound, unless clipped); contraindications to the use of gonadotrophins; history of untreated endocrine disease **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH & hMG (n = 77) **Arm 2:** short antagonist plus rFSH (n = 75) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; ongoing pregnancy; cancellation; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** live birth; clinical pregnancy; ongoing pregnancy; cancellation; oocyte number; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript **Trial registration:** The EUDRACT number of the trial was 2013-000583-29, and the study was registered in clinicaltrials.gov (NCT01816321)

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Drakopoulos 2017 *(Continued)*

Registration date: 22 March 2013

Conflict of interest declaration: "P.D., N.L.V., N.A.V.H., A.V., M.T.H., M.C., A.T.L. and A.V.V. have no conflict of interest to report. C.B. has received unrestricted research grants from MSD and Ferring as well as honoraria for lectures from Abbott, MSD, Merck and Ferring. P.H. has received unrestricted research grants from MSD, Merck and Ferring as well as honoraria for lectures from Merck, MSD and IBSA. H.T. has received unrestricted research grants from MSD, Merck, Ferring, Cook, Roche Diagnostics, Besins International and Goodlife as well as consultation fees for research project in female infertility from Merck Finox, Abbott and ObsEva.N.P.P has received unrestricted research grants from MSD, Ferring, Roche Diagnostics and Besins International as well as honoraria for lectures from MSD, Merck and Ferring."

Funding: none sought

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - l w k of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgeme t
Random sequence generation (selection bias)	Low risk	"computer generat d randomization list".
Allocation concealment (selection bias)	Low risk	Centrally manage allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Ope label trial, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label" trial, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Twelve women were cancelled in group A (>10%) and seven in group B.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.
Other bias	Low isk	Trial conducted post-2010 and prospectively registered. Multicentre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Dravid 2015

Study characteristics

Methods	**Design:** randomised controlled trial

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Dravid 2015 *(Continued)*

	Country: India
	Language: English
	Setting: single centre
	Recruitment period: from 2012 to 2014
	Sample size (total randomised): 106
Participants	**Inclusion criteria:** predicted low ovarian response (basal serum AMH <1.2 ng/mL; AFC = 6) undergoing IVF/ICSI irrespective of age
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: predicted low respons
	Oocyte donors: no
	Cause of infertility: low ovarian reserve
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH & rLH (n = 54)
	Arm 2: short antagonist plus rFSH (n = 52)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: blastocyst (day 5+)
	Luteal phase support: unstated
Outcomes	**Outcomes reported** clin cal pregnancy
	Outcomes included in the meta-analysis: none
Notes	**Type of p licati n:** conference abstract
	Trial egistration: unstated
	Registratio date: -
	Conflict of interest declaration: unstated
	Fund g: unstated
	Author correspondence: none undertaken (author contact details not found)
	Calculations used to obtain absolute event numbers: yes
	Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement

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Dravid 2015 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective out omes port d.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed. PR calculated based on percentages. Out of 106 women randomi ed, ly 84 nderwent embryo transfer (attrition >10%).
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010 Registra ion timeline unstated. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted post-2010. Registration timeline unstated. Single centre study with plausible rec u tme t rates. Effect size difference lower than two-fold between trial arms.

Duijkers 1997

Study characteristics	
Methods	**Design:** randomised c trolled trial **Country:** The Nethe la ds **Language:** Engl h **Setting:** singl centre **Recruitm nt period:** unstated **Sample size (total randomised):** 18
Participants	**Incl sion criteria:** age 20-40 years; tubal pathology or unexplained infertility; normal endocrine serum pr file; no hormonal medication for at least two menstrual cycles prior to the study; no endometriosis; both ovaries present; no male subfertility **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no

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Duijkers 1997 *(Continued)*

Interventions	**Arm 1:** long agonist plus uFSH (n = 9) **Arm 2:** long agonist plus uFSH & uLH (ratio 3:1) (n = 9) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number; fertilisation rate; serum FSH, LH, ndrostenedione, testosterone, oestradiol, oestrone and progesterone concentrations **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute even numbers:** no **Inclusion in meta-analysis:** no (numbe of oocytes is the only outcome of interest reported, although expressed as median [range], ther for no meta-analysable; no author contact details found; unclear risk of selection and other biases, p mary eview outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgemen	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly divided".
Allocation concealment (selection bias)	Unclea risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (dete ion b as) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Number of cancelled cycles unstated.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.

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Duijkers 1997 *(Continued)*

Other bias	Unclear risk	Single centre study, timeline unstated. Conducted pre-2010.

Durnerin 2008

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** International (Denmark, France and Scotland) **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 146
Participants	**Inclusion criteria:** age 19-39 years; normal menstr al cycles (25–34 days); both ovaries present; BMI <28 kg/m^2 **Exclusion criteria:** PCOS; previous low respon e (<5 mature sized follicles in standard IVF) **Predicted response as stated by the triali ts:** un tated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity)**
Interventions	**Arm 1:** long agonist pl s rFSH & rLH (n = 75) **Arm 2:** lon agon t plus rFSH (n = 71) **Fertil sation method:** unstated **Embryo age at the time of transfer:** unstated **Lut al phase support:** variable
Outcomes	**Outc mes reported:** ongoing pregnancy; oocyte number; number of cleavage-stage embryos **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** "A number of the authors (RF, SGH, JNH, HL, LW, RY) declare that they have received financial support from MerckSerono in recent years." **Funding:** "The recombinant-human LH (Luveris) was supplied free of charge by MerckSerono, although the recombinant FSH (Gonal-F) was not. Central laboratory assessments of hormone values: the consumable costs of the hormone assays were covered by funds from Serono Ltd, UK."

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Durnerin 2008 *(Continued)*

Author correspondence: yes - r.fleming@udcf.gla.ac.uk (16 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"block randomized by centre in blocks of 10
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open label", subjective utcomes r ported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open label", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis pe formed. Nine patients discontinued treatment in the LH group, and three n the no LH group. Attrition >10% in the LH group.
Selective reporting (reporting bias)	Low risk	Trial onduc ed and published pre-2010. Selective reporting not detected.
Other bias	Low risk	T ial conducted pre-2010. Multicentre study. No concerns regarding validity of resu ts. Effect size difference lower than two-fold between trial arms. No other biases detected.

Ebrahimi 2017

Study characteristics

Methods	**Design:** randomised controlled trial **Cou try:** Iran **L nguage:** English **Setting:** single centre **Recruitment period:** March to August 2015 **Sample size (total randomised):** 70
Participants	**Inclusion criteria:** at least two of three features contemporaneously present in each patient: low ovarian response in the previous cycle (at least one previous failed IVF/ICSI cycle with conventional long agonist protocol and <4 four mature oocytes); decreased ovarian reserve defined as AFC <5-7 or AMH <1.1 ng/ml; age of participants' partner ≥40 years

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Ebrahimi 2017 *(Continued)*

	Exclusion criteria: metabolic or endocrine disorders including hyperprolactinaemia and hypo/hyperthyroidism; endometriosis; previous ovarian surgery; BMI >30 kg/m^2; azoospermia in the male partner **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus letrozole & rFSH (n = 35) **Arm 2:** short antagonist plus rFSH (n = 35) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage st ge (days 2-4 **Luteal phase support:** vaginal or rectal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cance lation; oocyte number **Outcomes included in the meta-analysis:** linica pregnancy; cancellation; oocyte number
Notes	**Type of publication:** published full tex manuscript **Trial registration:** IRCT20141019195 8N1 **Registration date:** 6 Februa y 2015 **Conflict of interest decl ration** none declared **Funding:** unstated **Author correspondence:** none undertaken **Calculatio s use to obtain absolute event numbers:** no **Inclu on in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additiona comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera tion (selection bias)	Low isk	"Random number generator".
Allocation concealm nt (selection bias)	Low risk	"Randomization sequence was concealed using sequentially numbered, opaque and sealed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blinded" study.

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Ebrahimi 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blinded" study.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Seven women cancelled in the letrozole group and 8 in the placebo group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. Selective reporting not detected.
Other bias	Low risk	Trial conducted post-2010 and prospectively gist red. Single centre study with plausible recruitment rates. Effect si difference lower than two-fold between trial arms.

Edelstein 1990

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomis d):** 37
Participants	**Inclusion criteria:** unstated **Exclusion criteria:** nstated **Predicted respo se as stated by the trialists:** unstated **Oocyte dono s:** no **Cause f in ertility:** various **Subgroup (ag :** no **S bgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 18) **Arm 2:** long agonist plus uFSH (n = 19) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; ongoing pregnancy; multiple pregnancy; oocyte number; number of embryos cryopreserved

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Edelstein 1990 *(Continued)*

	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not fo nd) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection and othe biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized sequentia ly".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Uns ated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low ri k	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unc ear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Edi-Osagie 1999

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** United Kingdom

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Edi-Osagie 1999 *(Continued)*

	Language: English
	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 38
Participants	**Inclusion criteria:** women undergoing COS for ART
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 15)
	Arm 2: short agonist plus rFSH (n = 23)
	Fertilisation method: unstated
	Embryo age at the time of transf r: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** live birt serum oestradiol, progesterone and LH levels; duration of stimulation; oocyte number; fertilisation rate clinical pregnancy
	Outcomes included n th meta-analysis: live birth
Notes	**Type of publicat on:** onference abstract
	Trial regi tion unstated
	Regi ration date: -
	Conflict of terest declaration: unstated
	Fu ding: unstated
	Auth r correspondence: none undertaken
	Calc lations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised", methodology unstated.

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Edi-Osagie 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Selective reporting not det cted
Other bias	Unclear risk	Single centre trial, unclea timeline Conducted pre-2010.

El Kassar 2017

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Egypt **Language:** English **Setting:** single centr **Recruitment period** February 2014 to March 2015 **Sample size (tot l randomised):** 60
Participants	**Inclu ion cri eria:** PCOS **Exclusion c iteria:** unstated **Pr dicted response as stated by the trialists:** predicted high response **Oocy e donors:** no **Cau e of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus letrozole & hMG (n = 30) **Arm 2:** short antagonist plus hMG (n = 30) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated

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El Kassar 2017 *(Continued)*

	Luteal phase support: unstated
Outcomes	**Outcomes reported:** oocyte number; miscarriage; OHSS **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbe** no **Inclusion in meta-analysis:** no (insufficient data n the abstr ct; author contact details not found) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgeme t
Random sequence generation (selection bias)	Unclear risk	"randomly allocated , methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unsta d.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Uns ted subjective outcomes reported (e.g., OHSS).
Blinding of outcome assessment (detection bias) All outcomes	Unclear r	Unstated, subjective outcomes reported (e.g., OHSS).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	Timeline and number of centres unclear. Conducted post-2010, registration status unclear.

El-Sahwi 2006

Study characteristics

Methods	**Design:** randomised controlled trial

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El-Sahwi 2006 *(Continued)*

	Country: Egypt
	Language: English
	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 160
Participants	**Inclusion criteria:** unstated
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 80)
	Arm 2: short antagonist plus hMG (n = 0)
	Fertilisation method: ICSI
	Embryo age at the time of transfe unst ted
	Luteal phase support: unsta ed
Outcomes	**Outcomes reported:** OHSS; cl al pregnancy; cancellation; oocyte number
	Outcomes include in the meta-analysis: OHSS
Notes	**Type of publicat on:** conference abstract
	Trial registra on: un tated
	Registr tion date: -
	Conflict of int rest declaration: unstated
	F ding: unstated
	A thor correspondence: none undertaken (author contact details not found)
	Calc lations used to obtain absolute event numbers: yes
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement

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El-Sahwi 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"randomly divided (opaque envelopes)".
Allocation concealment (selection bias)	Unclear risk	"opaque envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if ITT analysis performed. C nical pregnancy event numbers calculated from percentages. Loss to fol w-up nstated.
Selective reporting (reporting bias)	Low risk	Trial conducted and publi hed pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline un ated. Effect size difference lower than two-fold between trial arms. No other bi ses detected.

Engel 2003

Study characteristics	
Methods	**Design:** randomised c trolled trial **Country:** France **Language:** Engl h **Setting:** singl centre **Recruitm nt period:** May 1999 to February 2000 **Sample size (total randomised):** 10
Participants	**Incl sion criteria:** age 18-39 years; normal menstrual cycles (24–35 days) with intra-individual variati n of no more than 3 days; ≤3 IVF procedures since the last pregnancy; normal uterine cavity **Excl sion criteria:** PCOS; severe endometriosis; FSH ≥10 IU/l **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no

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Engel 2003 *(Continued)*

Interventions	**Arm 1:** short antagonist plus clomifene citrate & hMG (n = 5) **Arm 2:** short antagonist plus clomifene citrate & rFSH (n = 5) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** live birth; OHSS; oocyte number **Outcomes included in the meta-analysis:** live birth; OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - joergbengel@ otmail.com (16 September 2021) **Calculations used to obtain absolute event umbers:** no **Inclusion in meta-analysis:** yes (sensitivity an lysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Suppo t for judgement
Random sequence generation (selection bias)	Unclear risk	Uns ated.
Allocation concealment (selection bias)	Unclear isk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Open study", however only objective outcomes used in the meta-analysis.
Blinding of outcome assessment (detectio bias) All outcomes	Low risk	"Open study", however only objective outcomes used in the meta-analysis.
Incomplete outcom data (attrition bias) All outcomes	High risk	ITT performed. One loss to follow-up and two cancellations due to low response. Attrition at least 10% per group.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Engel 2003 *(Continued)*

Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

EUCTR2004-001503-36-ES 2004

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** January 2005 to Novembe 2006 **Sample size (total randomised):** 131
Participants	**Inclusion criteria:** age 35-40 years; BMI 18-30 kg/m^2; baseline FSH ≤10 IU/l; baseline LH and oestradiol within local laboratory range; long GnRH agonist protocol; presence of both ovaries and uterine cavity able to sustain pregnancy; clomifene or go adotr phin washout >30 days prior to starting GnRH agonist; confirmed absence of pregnancy; signed informed consent **Exclusion criteria:** blood borne vir ses >2 previous ART cycles; unexplained gynaecological bleeding; PCOS; contraindications to pregnancy act ve substance abuse **Predicted response as stated y the ialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian response **Subgroup (age):** no **Subgroup (BMI)** yes (<30 kg/m^2) **Subgroup (et nicity)** no
Interventions	**Arm 1:** lo agonist plus rFSH (n = 68) **Arm 2:** long agonist plus rFSH & rLH (n = 63) **Fe ilisation method:** unstated **Em ryo age at the time of transfer:** unstated **Lut al phase support:** unstated
Outcomes	**Outcomes reported:** mature oocyte number; oocyte number; fertilisation rate; embryo quality; implantation rate; biochemical pregnancy; clinical pregnancy; duration of stimulation; total dose of gonadotrophins; serum oestradiol levels on trigger injection day; OHSS (rates not possible to extract for meta-analysis) **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** trial registration record **Trial registration:** EUCTR2004-001503-36-ES

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EUCTR2004-001503-36-ES 2004 *(Continued)*

Registration date: 14 October 2004

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection and other biases; not possible to meta-analyse OHSS rates)

Additional comments: data extracted from trial report; no publish d man script found

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, howeve o ly objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, h wever only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear isk	Trial conducted pre-2010. Single centre study with plausible recruitment rates.

EUCTR2010-019411-37-DE 20 0

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Germany **Language:** English **Setting:** multicentre **Recruitment period:** October 2010 to January 2013 **Sample size (total randomised):** 124

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EUCTR2010-019411-37-DE 2010 *(Continued)*

Participants	**Inclusion criteria:** age 34-42 years; tubal or unexplained infertility; BMI 18-28 kg/m^2; normal pelvic ultrasound (showing two ovaries, no ovarian or uterine abnormalities [ovarian cysts caused by endometriosis, myoma indicating surgery, distorted cavity); ≤2 previous gonadotrophin stimulated cycles of IVF or ICSI in the history of infertility treatment; ≥3 consecutive ovulatory menstrual cycles of 24-35 days; documented evidence of ovulatory cycles within the previous 12 months prior to randomisation; no fertility stimulating drugs within the previous three months; sperm of male partner classified as normal according to WHO 2010 criteria within the previous year; negative urine beta hCG pregnancy test; clinically normal baseline haematology, clinical chemistry, urinalysis values; negative serum Hepatitis B Surface Antigen (HBsAg), HCV and HIV antibody tests within the last 6 months; normal baseline endocrine blood tests **Exclusion criteria:** any clinically relevant systemic disease (e.g., insulin-dependent diabetes mellitus); history of or current endocrine disease (excluding treated hypot yroidism), cluding PCOS and hyperprolactinaemia; history of coagulation disorders; persistent ovarian ysts (>3 months); contraindications to the use of gonadotrophins or GnRH antagonists; histo y f hype sensitivity to any of the constituents of the study medication or related compounds; history of al ohol abuse (>30 units per week on a regular basis); history of chemo- or radiotherapy; current y breast-feeding, pregnant or with a contraindication to pregnancy; diagnosed with low ov rian res onse < 3 oocytes) to prior gonadotrophin stimulated ART cycle; previous severe OHSS; tria drug admin stration within the previous 30 days **Predicted response as stated by the trialists:** uns ated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus clomife e citrate & hMG (n = 5) **Arm 2:** short antagonist plus clomifene citrate & rFSH (n = 5) **Fertilisation method:** unstated **Embryo age at t e tim of transfer:** unstated **Luteal phase support:** vaginal progesterone
Outcomes	**Outco es eported:** OHSS; clinical pregnancy; ongoing pregnancy; oocyte number **Outcomes inc uded in the meta-analysis:** OHSS
Notes	**Ty e of publication:** trial report **Tr l registration:** EUCTR2010-019411-37-DE **Reg stration date:** 2 July 2010 **Conflict of interest declaration:** unstated **Funding:** "Sponsored by Ferring." **Author correspondence:** none undertaken (author contact details not found) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

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EUCTR2010-019411-37-DE 2010 *(Continued)*

Additional comments: -

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open label", subjective outcomes repor ed.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open label", subjective utcomes ported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to obtain absolute event numbers. Eighteen women experienced protocol violations (14 in the hMG group and 4 in the rFSH group) Attrition >10% in the hMG group.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. All outcomes repo ted as stated in the registration
Other bias	Low risk	Trial cond ted post-2010 and prospectively registered. Single centre study with pla sible recruitment rates. Effect size difference lower than two-fold betwee trial arms.

Fabregues 2006

Study characteristics	
Methods	**Design:** rand mised controlled trial **Country:** Spain **La guage:** English **Setti g:** single centre **Rec itment period:** November 2003 to September 2004 **mple size (total randomised):** 120
Participants	**Inclusion criteria:** age 35-42 years; regular menstrual cycles (24–34 days); normal ovaries; no previous ovarian surgery; no ovarian failure; no hormone therapy within the previous six months **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various

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Fabregues 2006 *(Continued)*

	Subgroup (age): yes (≥35 years)
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 60)
	Arm 2: long agonist plus rFSH (n = 60)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; multiple pregnancy; miscarriage; oocyte number
	Outcomes included in the meta-analysis: OHSS
Notes	**Type of publication:** published full-text manusc pt
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: "Supported in part by grants fro th Instituto de Salud Carlos III (RCMN C03/08) and the Comissionat per a Universitat i Rece ca Generalitat de Catalunya (2001SGR 00372 and 2005SGR 00573)."
	Author correspondence: yes - jbalasc @ub.edu (16 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/ r OHSS])
	Additional commen -

Risk of bias

Bias	Autho ' ju gement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization table".
Allocation concealment (selection bias)	Unclea risk	"Sealed envelopes for the randomization list were used", although unclear if SNOSE.
Blinding of partic pants and personnel (perfor mance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias)	Low risk	ITT analysis performed. A total of ten women (five in each group) had cancelled stimulation. Attrition <10% in both trial arms.

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Fabregues 2006 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Fabregues 2011

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** January 2007 to February 2008 **Sample size (total randomised):** 187
Participants	**Inclusion criteria:** age >35 years **Exclusion criteria:** hormone therapy including gonadotrophins, for at least six months preceding the study **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility** various **Subgroup (age)** yes (≥3 years) **Subgroup (B I):** yes (<30 kg/m^2) **Subgr up (thnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 62) **A 2:** long agonist plus rFSH & rLH (n = 125) - two arms merged (see additional comments) **Fe ilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; multiple pregnancy; miscarriage; pregnancy rate; follicle number; serum oestradiol level; total gonadotrophin dose; oocyte number; mature oocyte number; embryo number; cancellation; implantation rate **Outcomes included in the meta-analysis:** OHSS; clinical pregnancy; multiple pregnancy; miscarriage; oocyte number
Notes	**Type of publication:** published full-text manuscript

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Fabregues 2011 *(Continued)*

Trial registration: unstated

Registration date: -

Conflict of interest declaration: unstated

Funding: "This work was supported, in part, by a grant from the Agencia de Gestio ´ d ´ Ajuts Universitaris i de Recerca - Generalitat de Catalunya (2009SGR 1099)."

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: yes

Inclusion in meta-analysis: yes (primary analysis - low risk of selec on and other biases)

Additional comments: A total of 187 women undergoing a long dow regulati n protocol were randomised to COS using rFSH alone (group1, n = 62), rFSH with LH 7 5 IU (group 2, n = 62) or rFSH with rLH 75 IU (group 3, n = 63). For the purposes of the meta-ana ysis, gro ps 2 and 3 were merged.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated simple randomization table".
Allocation concealment (selection bias)	Low risk	"Concealment of tr atme t allocaiton was achieved with the use of sealed opaque envelop each containing a unique study number and prepared independently by a secretary".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, oweve only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Six women were lost to follow-up in group 1; eight in group 2; and eight in group 3. Therefore attrition >10% in all trial arms.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Single centre trial with plausible recruitment rates. Study conducted pre-2010.

Fenichel 1988

Study characteristics

Methods

Design: randomised controlled trial

Country: France

Language: French

Setting: single centre

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Fenichel 1988 *(Continued)*

	Recruitment period: unstated
	Sample size (total randomised): 30
Participants	**Inclusion criteria:** age <38 years; tubal factor; normal SFA; ovulatory menstrual cycles; <3 previous ART cycles
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: tubal
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** clomifene citrate without pituitary suppre sion (n = 10
	Arm 2: long agonist plus hMG (n = 10)
	Arm 3: agonist flare plus hMG (n = 10)
	Fertilisation method: unstated
	Embryo age at the time of transfer: cleavage tage (days 2-4)
	Luteal phase support: hCG
Outcomes	**Outcomes reported:** clinica preg ancy; oocyte number
	Outcomes included in the met -analysis: none
Notes	**Type of publication** pub ished full-text manuscript
	Trial registratio : un tated
	Registrat date
	Conf ct of in erest declaration: unstated
	Funding: Decapeptyl supplied by Beaufour."
	Au hor correspondence: none undertaken (author contact details not found)
	Calculations used to obtain absolute event numbers: no
	Incl sion in meta-analysis: no (unclear risk of selection bias; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.

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Fenichel 1988 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Three women cancelled in the clomifene citrate plus hMG group. Attrition = 10% in this group.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010 Sele tive re orting not detected.
Other bias	Low risk	Trial conducted pre-2010 S ngle entre tudy with plausible recruitment rates. No concerns regarding v lidity of re ults. Effect size difference lower than two-fold between trial arms. o other bia es detected.

Ferrareti 1996

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Italy **Language:** English **Setting:** single centre **Recruitment perio :** Ap il t December 1995 **Sample size (to al randomised):** 160
Participants	**Inclusi n cri ria:** ag <38 years; normo-ovulatory **Exclus n c iteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **C use of infertility:** unstated **Sub roup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus uFSH (n = 80) **Arm 2:** long agonist plus uFSH & rFSH (n = 80) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated

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Ferrareti 1996 *(Continued)*

	Luteal phase support: unstated
Outcomes	**Outcomes reported:** live birth (expressed as percentage per embryo transfer, therefore unable to include in the meta-analysis); oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (insufficient data n the abstr ct; no author contact details found) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgem nt
Random sequence generation (selection bias)	Unclear risk	"randoml allocated", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Uns ated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Un lear risk	Unclear whether ITT analysis performed.
Selective reporting (reporting bias)	Uncl ar risk	Selective reporting not detected.
Other bias	Unclear risk	Single centre study with plausible recruitment rates. Study conducted pre-2010.

Ferraretti 2004

Study characteristics

Methods	**Design:** randomised controlled trial

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Ferraretti 2004 *(Continued)*

	Country: Italy
	Language: English
	Setting: single centre
	Recruitment period: January 2002 to April 2003
	Sample size (total randomised): 134
Participants	**Inclusion criteria:** age ≤37 years; hyporesponsiveness to FSH; BMI ≤ 27 kg/m^2; normo-ovulatory cycles; no ovarian stimulation during the past 6 months; normal uterine cavity as checked by hysteroscopy; presence of both ovaries; and normal karyotypes in both partners
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: predicted low resp nse
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 54)
	Arm 2: long agonist plus rFSH & rLH (n 54)
	Arm 3: long agonist plus hMG rFSH (n = 26)
	Fertilisation method: unstated
	Embryo age at the time of tran er: cleavage stage (days 2-4)
	Luteal phase supp rt: i tramuscular progesterone
Outcomes	**Outcomes rep rted:** live birth; miscarriage; cancellation; oocyte number; number of cleavage-stage embryos n mber f embryos cryopreserved
	Outc mes in luded in the meta-analysis: live birth
Notes	**Type of pub cation:** published full-text manuscript
	Tr al registration: unstated
	Regist ation date: -
	Conf ict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - annapia.ferraretti@sismer.it (16 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -
Risk of bias	

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Ferraretti 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The randomization in groups A and B was on a one-to-one basis, whereas in group C it was performed by consecutive numbers: for every two patients entering groups A and B, one patient was enrolled in group C."
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective o tcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. ight wome (four in group A and four in group C) did not complete the study. A rition >1 % in group C.
Selective reporting (reporting bias)	Low risk	Trial conducted and p blished pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre 2 10. Single centre study with plausible recruitment rates. No concer s regarding validity of results. Effect size difference lower than two-fold betw en trial rms. No other biases detected.

Ferrari 2006

Study characteristics	
Methods	**Design:** random sed controlled trial **Countr :** Italy **Langu ge:** English **Setting:** single centre **Recruitment period:** November 2003 to January 2004 **S mple size (total randomised):** 60
Participants	**Inclusion criteria:** age 20-39 years; regular menstrual cycles (26–34 days); BMI 20-25 kg/m^2; baseline FSH levels <10 IU/l; baseline serum oestradiol >45 pg/ml **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2)

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Ferrari 2006 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 30) **Arm 2:** short antagonist plus rFSH (n = 30) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - bruno.ferra i@unipr.it (16 September 2021) **Calculations used to obtain absolute ev nt numbers:** no **Inclusion in meta-analysis:** no (u clea risk of selection bias [allocation concealment unstated]; primary review outcomes not eported) **Additional comments:** -

Risk of bias

Bias	**Authors' judgemen**	**upport for judgement**
Random sequence generation (selection bias)	Low risk	computer-generated randomisation list".
Allocation concealment (selection bias)	Uncl r risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detec ion bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Ferrari 2006 *(Continued)*

Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Firouzabadi 2010

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** December 2007 to January 2009 **Sample size (total randomised):** 235
Participants	**Inclusion criteria:** age <35 years; first cycle of the ART; basal FSH <10 IU/l **Exclusion criteria:** previous IVF or ICSI; hy erprolactinaemia; hyperthyroidism; hypothyroidism; uterine abnormality; severe endometriosis; soli ary ov ry **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** yes (<35 years **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** lon agon t plus rFSH (n = 117) **Arm 2** short antagonist plus rFSH & hMG (n = 118) **Fertilisati n method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Lute l phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; ongoing pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - ahmadishahnaz2005@yahoo.com (16 September 2021)

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Firouzabadi 2010 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomized schedules".
Allocation concealment (selection bias)	Unclear risk	"sealed in envelopes and handed to patients , unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes re orted
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not stric y performed but possible to extract absolute event numbers. Seventee women did not complete treatment in the agonist group, and eight in t e a tagonist group.Attrition rate >10% in the GnRH agonist arm.
Selective reporting (reporting bias)	Low risk	Tria conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Fisch 1995

Study characteristics

Methods	**D sign:** randomised controlled trial **Country:** International (Israel, Switzerland and United States of America) **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 20
Participants	**Inclusion criteria:** age 18-38 years; BMI <26.7 kg/m^2; normal baseline hormonal profile; no PCOS; normal uterine cavity confirmed by hysteroscopy or hysterography; no endometriosis detected laparoscopically

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Fisch 1995 *(Continued)*

	Exclusion criteria: >3 previous IVF cycles; previous low ovarian response to standard COS protocols; male factor infertility
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus uFSH (n = 10)
	Arm 2: long agonist plus rFSH (n = 10)
	Fertilisation method: unstated
	Embryo age at the time of transfer: unstated
	Luteal phase support: intramuscular progesterone
Outcomes	**Outcomes reported:** OHSS; cancellation; oocy e number
	Outcomes included in the meta-analysis: OHSS
Notes	**Type of publication:** published full tex manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest decl ration unstated
	Funding: unstated
	Author correspondence: none undertaken (author contact details not found)
	Calculatio s use to obtain absolute event numbers: no
	Inclu on in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcom s [l ve birth and/or OHSS])
	Additional co ments: -

Risk of bias

Bias	Aut ors' judgement	Support for judgement
Random sequence genera-tion (selection b as)	Unclear risk	"allocated at random", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (perfor-mance bias) All outcomes	Low risk	Unstated, however only objective outcomes included in the meta-analysis.

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Fisch 1995 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes included in the meta-analysis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single cent e study Recruitment rates unclear as study timeline unstated.Effect size differe ce lower t an two-fold between trial arms. No other biases detected.

Fleming 1996

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United Kingdom **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomis d):** 60
Participants	**Inclusion criteria:** age 28-40 years; tubal infertility; normal menstrual cycles **Exclusion criteria:** nstated **Predicted respo se as stated by the trialists:** unstated **Oocyte dono s:** no **Cause f in ertility:** tubal **Subgroup (ag :** no **S bgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 20) **Arm 2:** long agonist plus uFSH (n = 40) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis:** none

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Fleming 1996 *(Continued)*

Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** "Supported by Serono UK Ltd." **Author correspondence:** none undertaken (author contact details not found) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias; prim ry review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	stated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Fluker 2001

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** International (Canada and United States of America) **Language:** English **Setting:** multicentre

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Fluker 2001 *(Continued)*

	Recruitment period: unstated
	Sample size (total randomised): 313
Participants	**Inclusion criteria:** age 18-39 years; normal menstrual cycles (24-35 days); normal SFA (WHO criteria or Kruger's criteria)
	Exclusion criteria: serum FSH or LH levels ≥10 IU/l
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 208)
	Arm 2: long agonist plus rFSH (n = 105)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: unsta ed
	Luteal phase support: progesterone (variable route)
Outcomes	**Outcomes reported:** OHSS
	Outcomes included in the meta-a alysis: OHSS
Notes	**Type of publication:** publ hed f ll-text manuscript
	Trial registration: unsta ed
	Registration date: -
	Conflict f teres declaration: unstated
	Fund ng: unstated
	Author corr spondence: none undertaken (author contact details not found)
	Ca culations used to obtain absolute event numbers: no
	Inclus on in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary ou omes [live birth and/or OHSS])
	Add tional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized".
Allocation concealment (selection bias)	Unclear risk	Unstated.

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Fluker 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	"open label" trial, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open label" trial, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. A total of 30 women dropped out in the antagonist group, and 14 in the agonist group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010 Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010 Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Fornaro 2007

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 73
Participants	**Inclusion criteria:** age 20-39 years; no relevant systemic disease; tubal factor or unexplained infertility; BMI 1 -26 kg m^2; normal early follicular phase parameters **Exclusion criteria:** hyperprolactinaemia; PCOS; current or past diseases that affect the ovaries or the secretion, clearance or excretion of gonadotrophins or sex steroids; endometriosis; previous COS cycles in which <3 oocytes were retrieved; male factor **Predicted response as stated by the trialists:** predicted normal response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 37) **Arm 2:** short antagonist plus rFSH (n = 36) **Fertilisation method:** IVF

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Fornaro 2007 *(Continued)*

	Embryo age at the time of transfer: cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** "Supported by grants from "Ministero dell'Istruzio e, del Università e della Ricerca" (PRIN 2004, prot. 2004061475_002)." **Author correspondence:** yes - nicola.colacurci@ nina2.it (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support or j dgement
Random sequence generation (selection bias)	Low risk	"comput r-generated randomization list that used random numbers".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	nstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Foulot 1988

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** France **Language:** French **Setting:** single centre **Recruitment period:** June to October 1987 **Sample size (total randomised):** 100
Participants	**Inclusion criteria:** unstated **Exclusion criteria:** PCOS **Predicted response as stated by the trialists:** un tated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 0) **Arm 2:** agonist flare plus hMG (n 50) **Fertilisation method:** unstated **Embryo age at the tim of transfer:** unstated **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes repor ed:** clinical pregnancy; miscarriage; oocyte number **Outcomes in uded in the meta-analysis:** none
Notes	**Type of pu lication:** published full-text manuscript **Tr al registration:** unstated **Regi tration date:** - **Con ict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not found) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -
Risk of bias	

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Foulot 1988 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random draw.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed b t possible to extract absolute event numbers. Five cycles cancelled in the lon protocol, and four cancelled in the short protocol (total = 9). Attriti n = 10% n the long protocol arm.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre 2010. Single centre study with plausible recruitment rates. No concerns regard validity of results. Effect size difference lower than two-fold between tr al arms. No other biases detected.

Franco 2000

Study characteristics	
Methods	**Design:** randomised c ntrol ed trial **Country:** Brazil **Lang age:** English **Setting:** s gle centre **Re ruitment period:** July 1997 to June 1998 **Sample size (total randomised):** 120
Participants	**Inclusion criteria:** age ≤37 years; male infertility **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** male factor **Subgroup (age):** no **Subgroup (BMI):** no

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Franco 2000 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 60) **Arm 2:** long agonist plus uFSH (n = 60) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** hCG or progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertake (uthor contact details not found) **Calculations used to obtain absolute ev nt numbers:** no **Inclusion in meta-analysis:** yes (sensit vity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS] **Additional comments:** -

Risk of bias

Bias	**Authors' judgemen**	**upport for judgement**
Random sequence generation (selection bias)	Low risk	random, by drawing lots, using a randomization table previously elaborated for the study".
Allocation concealment (selection bias)	Uncl r risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detec ion bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Franco 2000 *(Continued)*

Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Franco 2003

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Brazil **Language:** Portuguese **Setting:** single centre **Recruitment period:** January to June 2002 **Sample size (total randomised):** 20
Participants	**Inclusion criteria:** age ≤37 years old **Exclusion criteria:** unstated **Predicted response as stated by the t alists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicit):** no
Interventions	**Arm 1:** short ant gonist plus rFSH (n = 14) **Arm 2:** long a onist plus rFSH (n = 6) **Fertili atio method:** ICSI **Embryo age the time of transfer:** cleavage stage (days 2-4) **Lu eal phase support:** unstated
Outcomes	**O tcomes reported:** miscarriage; ectopic pregnancy; oocyte number **Out omes included in the meta-analysis:** miscarriage; ectopic pregnancy; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - crh@crh.com.br (16 September 2021)

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Franco 2003 *(Continued)*

Calculations used to obtain absolute event numbers: yes

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	As confirmed by the authors on 20/09/2021: "Randomization: A double randomization process was used. First, a computer-generated table (first randomization) indicated which ovulation induction protocol (GnRH-a or GnRHant) was assigned. Then, lots were drawn (second randomization) to determine to which case that specific patient would correspond (i.e., case #1 or case #30).".
Allocation concealment (selection bias)	Low risk	As confirmed by the authors on 20/09/2021: "A registered nurse not involved in the recruiting, assessment or treatment of the patients was the responsible to kept the a computer generated table with the case numbers in a safe locked location and carried out the drawn lots were to determine the case number of each patient. No investigator was involved in the allocation process.".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Unclear if ITT analysis strictly performed, however possible to obtain absolute event numbers from published data. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Freitas 2004

Study characteristics

Methods	**Design:** randomised controlled trial
	Country: Brazil
	Language: English
	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 47

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Freitas 2004 *(Continued)*

Participants	**Inclusion criteria:** unstated **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 24) **Arm 2:** long agonist plus rFSH (n = 23) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis** o e
Notes	**Type of publication:** conference abst act **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not found) **Calcul tions sed to obtain absolute event numbers:** no **Inclusio i meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequen e ge era-tion (selection bias)	Unclear risk	"randomly allocated".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (perfor-mance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.

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Freitas 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear if ITT analysis performed but possible to extract absolute event numbers. Three women were cancelled in the antagonist group, and one in the agonist group. Attrition >10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single cent e study Recruitment rates unclear as study timeline unstated. Effect size differ ce lower han two-fold between trial arms. No other biases detected.

Friedler 2006

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Israel **Language:** English **Setting:** single centre **Recruitment period:** July to D cemb 2003 **Sample size (total randomis d):** 78
Participants	**Inclusion criteria:** age <35 years; normo-ovulatory cycles; male or tubal infertility **Exclusion criteria:** nd crinopathy, PCOS, baseline FSH >10 IU/ml **Predicted respo se as stated by the trialists:** predicted normal response **Oocyte dono s:** no **Cause f in ertility:** various **Subgroup (ag :** yes (<35 years) **S bgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 40) **Arm 2:** long agonist plus rFSH (n = 38) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; multiple pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** none

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Friedler 2006 *(Continued)*

Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - ivfunitdoc@asaf.health.gov.il (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias [alloc tion conc alment unstated]; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomization list"
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated howeve only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Three women dropped out in the antagonist group, and two women in the agonist group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Frydman 1988

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** France **Language:** English

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Frydman 1988 *(Continued)*

	Setting: multicentre
	Recruitment period: December 1995 to December 1996
	Sample size (total randomised): 278
Participants	**Inclusion criteria:** unstated
	Exclusion criteria: low ovarian response
	Predicted response as stated by the trialists: unselected population
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG & uFSH (n = 94)
	Arm 2: agonist flare plus hMG & uFSH (n = 92)
	Fertilisation method: unstated
	Embryo age at the time of transfer: u stated
	Luteal phase support: oral dydrogeste one
Outcomes	**Outcomes reported:** ongoing regn ncy; oocyte number
	Outcomes included in the m ta-ana ysis: none
Notes	**Type of publication:** published full-text manuscript
	Trial registration: nst ted
	Registration date: -
	Conflic of in erest d claration: unstated
	Funding: u stated
	Author correspondence: none undertaken (author contact details not found)
	C culations used to obtain absolute event numbers: no
	In lusion in meta-analysis: no (unclear risk of selection bias; primary review outcomes not reported)
	Add ional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were prospectively randomized between the two treatment groups.".
Allocation concealment (selection bias)	Unclear risk	Unstated.

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Frydman 1988 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Loss to follow-up <10% in all trial arms.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Study conduted pre-2010 S ngle entre rial, recruitment rates unstated.

Frydman 2000

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** France **Language:** English **Setting:** single centre **Recruitment period:** unst ted **Sample size (total randomised):** 186
Participants	**Inclusion criter a:** age 38 years; normal FSH, LH, prolactin and testosterone; <10 follicles on each ovary on pelvic u rasound; tubal factor, mild endometriosis, male factor, unexplained infertility; normal ute us and ovaries; <4 previous IVF cycles; no treatment with clomifene citrate or gonadotrophins withi 1 mon h of the treatment cycle **Exclusion riteria:** systemic disease; contraindication to pregnancy; BMI >30 kg/m^2; previous OHSS; previous poor response; abnormal gynaecological bleeding; azoospermia in the male partner **P dicted response as stated by the trialists:** predicted normal response **Oo yte donors:** no **Cau e of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 139) **Arm 2:** long agonist plus uFSH (n = 139) **Fertilisation method:** IVF or ICSI

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Frydman 2000 *(Continued)*

	Embryo age at the time of transfer: cleavage stage (days 2-4) **Luteal phase support:** oral micronised progesterone
Outcomes	**Outcomes reported:** live birth; OHSS; ongoing pregnancy; miscarriage; oocyte number; number of cleavage-stage embryos **Outcomes included in the meta-analysis:** live birth; OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (auth r contact details not found) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support or j dgement
Random sequence generation (selection bias)	Unclear risk	"random ed (…) according to identification number" - unclear if medical recor number or randomisation number.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	double-blind" study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" study.
Incomplete outcome data (attrition bias) All outcomes	H h risk	ITT analysis performed. A total of 11 women were cancelled in the rFSH group and 26in the uFSH group. Attrition >10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Fujimoto 2014

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Japan **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 89
Participants	**Inclusion criteria:** low-responding women; baseline FSH >10 mIU/ml; AFC <7; previous low response to ART treatment (<5 retrieved oocytes) **Exclusion criteria:** age >45 years; >3 previous ART cycles **Predicted response as stated by the trialists:** p edicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus clomif e citrate & hMG (n = 44) **Arm 2:** short antagonist plus hMG (n 45) **Fertilisation method:** unsta d **Embryo age at the ime of transfer:** unstated **Luteal phase su port** unstated
Outcomes	**Outcomes re orted** serum oestradiol level; follicle number; oocyte number; fertilisation rate; total gonadotroph n dose and cost; cancellation; live birth; cumulative live birth **Outcomes ncluded in the meta-analysis:** live birth
Notes	**Type of publication:** conference abstract **Trial gistration:** unstated **Regi tration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

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Fujimoto 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., cancellation).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes repo ted (e.g., cancellation).
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear whether ITT analy is performed. Attrition rate >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Selective reporting n t detected.
Other bias	Unclear risk	Single centre s udy, timeline not stated. No other sources of bias identified.

Fusi 2020

Study characteristics

Methods	**Design:** randomi ed ontro ed trial **Country:** I ly **Lang age:** English **Setting:** si gle centre **Re ruitment period:** March 2016 to June 2019 **Sample size (total randomised):** 409
Participants	**Inclusion criteria:** age >40 years; <3 oocytes in previous cycle; AFC <5; AMH <1.1 ng/ml **Exclusion criteria:** BMI <18 or >30 kg/m^2; FSH >20; endometriosis grade IV; severe male factor **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** yes (≥35 years) **Subgroup (BMI):** no

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Fusi 2020 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 137) **Arm 2:** short antagonist plus rFSH & rLH (n = 136) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** ongoing pregnancy; cancellation;oocyte number **Outcomes included in the meta-analysis:** ongoing pregnancy; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** EudraCT2015–002817-31 **Registration date:** 2015 **Conflict of interest declaration:** none declared **Funding:** "The funding for analyzing the data nd writing the manuscript were obtained from the budget for Division of the Hospital Papa Giovanni XXIII." **Author correspondence:** yes - ffusi@asst-pg23.it (16 September 2021) **Calculations used to obtain absolute vent numbers:** no **Inclusion in meta-analysis** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	**Authors' judgemen**	**upport for judgement**
Random sequence generation (selection bias)	Low risk	computer-generated randomization sheet".
Allocation concealment (selection bias)	Low sk	"The doctor who prepared the therapy only knew the group assigned to the patient just before consultation", as per correspondence with Dr Francesco Fusi on 16/09/2021.
Blinding of participants and personnel (performance bias) All outcomes	Hi h risk	"open study", subjective outcomes reported.
Blinding of outc me assessment (detecti n bias) All outcomes	High risk	"open study", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Thirteen women cancelled in group 1; six in group 2; and nine in group 3 (total = 28). Attrition rate <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.

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Fusi 2020 *(Continued)*

Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Galera 2006

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 40
Participants	**Inclusion:** PCOS according to Rotterdam criteria **Exclusion criteria:** unstated **Predicted response as stated by the t alists:** predicted high response **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicit):** no
Interventions	**Arm 1:** long agonist plus FSH (n = 20) **Arm 2:** hort ntagonist plus rFSH (n = 20) **Fertili atio method:** unstated **Embryo age the time of transfer:** unstated **Lu eal phase support:** unstated
Outcomes	**O tcomes reported:** serum oestradiol, progesterone, testosterone, FSH and LH levels; pregnancy rate; OHS ; cancellation **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken

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Galera 2006 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (insufficient data in the abstract; author contact details not found)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised into two groups", methodology u stated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes repo ted (OHSS).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (OHSS).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unstated.
Selective reporting (reporting bias)	Unclear risk	Select ve reporting not detected.
Other bias	Unclear risk	S dy timeline unclear. Conducted pre-2010.

Gallego 2003

Study characteristics

Methods	**Design:** ra domised controlled trial **Co ntry:** Spain **Language:** Spanish **Set ng:** single centre **R cruitment period:** March 1999 to March 2001 **Sample size (total randomised):** 100
Participants	**Inclusion criteria:** age <40 years; BMI 18-29 kg/m^2; first cycle of IVF; basal FSH <10 mIU/ml; day 3 oestradiol <80 pg/ml **Exclusion criteria:** PCOS; severe male factor **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no

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Gallego 2003 *(Continued)*

	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 50)
	Arm 2: long agonist plus uFSH (n = 50)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; miscarriage; cancellatio ; cyte n mber
	Outcomes included in the meta-analysis: OHSS
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes galleg @urh.info (16 September 2021)
	Calculations used to obtain absolute event numbers: yes
	Inclusion in meta-analysis: yes ensitivity analysis - including all studies reporting on the primary outcomes [live birth and/ r OHSS])
	Additional commen s -

Risk of bias

Bias	Auth rs' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random numbers table".
Allocation concealment (selection bias)	Unclear risk	"the clinician would assign the next available number to new study recruits".
Blinding of partic pants and personnel (erformance bias) All outcomes	nclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers from percentages. Six women in the rFSH group and three in the uFSH

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Gallego 2003 *(Continued)*

		group were excluded from the study. There was one cancelled cycle in the rFSH group and two in the uFSH group (total = 12). Attrition >10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Garcia-Velasco 2011

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** June 2009 to May 20 0 **Sample size (total randomised):** 228
Participants	**Inclusion criteria:** age ≤38 years, egular normo-ovulatory menstrual cycles (26-35 days), BMI 18-30 kg/m^2, normal cycle day-3 basal serum hormones (FSH <10 IU/L and oestradiol <60 pg/ml) **Exclusion criteria:** previous varia surgery; low ovarian response (<5 oocytes) in a previous IVF-ICSI cycle; PCOS (Rotterdam criteria **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertil ty:** various **Subgr up (ag):** no **Subgro p (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 115) **Arm 2:** long agonist plus rFSH (n = 113) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; ongoing pregnancy; multiple pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** live birth; clinical pregnancy; ongoing pregnancy; multiple pregnancy; miscarriage; oocyte number
Notes	**Type of publication:** published full-text manuscript

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Garcia-Velasco 2011 *(Continued)*

Trial registration: NCT01157754

Registration date: 7 July 2010

Conflict of interest declaration: none declared

Funding: unstated

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection a d other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random numb r list".
Allocation concealment (selection bias)	Low risk	"Opaque, consecutively numbered envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstate however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	I T analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted pre- and up to 2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre- and up to 2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Ghadir 2005

Study characteri tics

Methods	**Design:** randomised controlled trial
	Country: United States of America
	Language: English
	Setting: single centre
	Recruitment period: unstated

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Ghadir 2005 *(Continued)*

	Sample size (total randomised): 37
Participants	**Inclusion criteria:** age 35-42 years; day 3 FSH ≤12 mIU/l **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** yes (≥35 years) **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short GnRH agonist flare plus rFSH (n = 20) **Arm 2:** short GnRH antagonist plus rFSH (n = 17) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number; fer ilisa ion rate; embryo aneuploidy rate; embryo number; clinical pregnancy **Outcomes included in the meta- na ysis** none
Notes	**Type of publication:** confere ce ab tract **Trial registration:** unstated **Registration date:** - **Conflict of inter st d claration:** unstated **Funding:** restr cted educational grant from Organon Pharmaceuticals, United States of America." **Auth r correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **In usion in meta-analysis:** no (insufficient data in the abstract; author contact details not found) **Addi onal comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence gen a-tion (selection bias)	Unclear risk	"randomised", methodology unclear.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias)	Low risk	Unstated, however only objective outcomes reported.

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Ghadir 2005 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed. Attrition unclear.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	Number of centres unclear. Trial timeline un tated. C nducted pre-2010.

Ghaebi 2018

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** Persian **Setting:** single centre **Recruitment period:** March 2013 to September 2015 **Sample size (total randomis d):** 10
Participants	**Inclusion criteria:** age 18-37 ye ; PCOS resistant to medical treatment **Exclusion criteria:** ge >38 years; tubal obstruction with hydrosalpinx; low response in previous IVF cycles; congenital uter abnormalities; heart disease, liver and kidney disease; ovarian cancer **Predicted response as stated by the trialists:** predicted high response **Oocyte dono s:** no **Cause of i fertility:** PCOS **Subgroup (age):** no **Subgroup (BMI):** no **Sub roup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 50) **Arm 2:** short antagonist plus rFSH (n = 46) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** OHSS; oocyte number

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Ghaebi 2018 *(Continued)*

	Outcomes included in the meta-analysis: OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - amirianm@mums.ac.ir (30 September 202) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - includi g al studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The randomisation me hod was performed using a packet in a package and by an independent pers ".
Allocation concealment (selection bias)	Unclear risk	."The rando i ation method was performed using a packet in a package and by an ind pen en person"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Uns ated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if ITT analysis was performed.
Selective reporting (reporting bias)	Unclear risk	Trial conducted post-2010. Trial registration status unstated.
Other bias	Unc ear risk	Trial conducted post-2010. Registration status unclear. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Ghasemzadeh 2019

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Iran

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Ghasemzadeh 2019 *(Continued)*

	Language: English
	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 114
Participants	**Inclusion criteria:** age 20-40 years; AFC>4; baseline FSH <15 IU/l
	Exclusion criteria: contraindication to COS; ovarian failure; endometriosis grades III and IV; severe male factor; donor oocyte cycles; FET cycles; known uterine anomalies; previous abortion or curettage; previous hysteroscopy, polypectomy, myomectomy or septum resection
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** progestogen plus rFSH (n = 57)
	Arm 2: short antagonist plus rFSH (n = 57)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfe unstated
	Luteal phase support: freeze all poli y
Outcomes	**Outcomes reported:** oocyte number
	Outcomes include in the meta-analysis: none
Notes	**Type of public t on:** published full-text manuscript
	Trial r gistra on: IRCT20110301005942N6
	Registr i n date: 3 June 2018
	Conflict of interest declaration: none declared
	F ding: unstated
	Au hor correspondence: yes - sahere_dopour@yahoo.com (23 February 2022)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Ghasemzadeh 2019 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Patients were enrolled in the study via block randomization".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"single-blinded controlled clinical trial", however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"single-blinded controlled clinical trial" how ver o ly objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly reported bu possible to extract absolute event numbers. Attrition rate >10% in both rial arms
Selective reporting (reporting bias)	Low risk	Selective reporting not de cted.
Other bias	Unclear risk	Study conducted post 010, recruitment timeline unstated. Registered "while recruiting" as per r l registry entry (IRCT20110301005942N6).

Gholami 2010

Study characteristics	
Methods	**Design:** randomised control d t ial **Country:** Italy **Language:** Engli h **Setting:** mu icentr **Recr tment period:** January 2008 to September 2008 **Sample siz (total randomised):** 115
Participants	**Inclusion criteria:** age <37 years; basal FSH <12 mIU/ml **xclus n criteria:** unstated **Pred cted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus uFSH (n = 62)

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Gholami 2010 *(Continued)*

	Arm 2: long agonist plus rFSH (n = 53) **Fertilisation method:** IVF **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - gholami@fastwebn t it (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of s lection selection bias; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support fo judgement
Random sequence generation (selection bias)	Unclear risk	Unst ted
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	U lear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	w risk	ITT analysis performed. One cycle cancelled in the GnRH agonist group; three cycles cancelled in the rFSH group (total = 4). Attrition rate <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Giles 2021

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** October 2017 to June 2019 **Sample size (total randomised):** 318
Participants	**Inclusion criteria:** healthy women aged 18-35 years; BMI 18–28 kg/m^2; regular menstrual cycles; no hereditary or chromosomal diseases; normal karyotype; no sexually transmitted infections; normal ovarian reserve; normal pelvic anatomy. **Exclusion criteria:** PCOS; chronic medical condition (e.g., diabetes, Crohn disease, thyroid disease, hepatitis B, or sexually transmitted infections); trial participation in the previous 3 months **Predicted response as stated by the trialists:** unstated **Oocyte donors:** yes **Cause of infertility:** N/A **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** progestogen plus rFSH (n = 161) **Arm 2:** short antagonist plus rFSH (n = 157) **Fertilisation method:** N/A **Embryo age at the time of transfer:** N/A **Luteal phase support:** N/A
Outcomes	**Outcomes reported:** cancellation; oocyte number; blastocyst number **Outcomes included in the meta-analysis:** cancellation; oocyte number; blastocyst number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT03300960 **Registration date:** 4 October 2017 **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - juan.giles@ivirma.com (3 March 2022) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases)

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Giles 2021 *(Continued)*

Additional comments: -

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A randomization table was obtained using a computer application".
Allocation concealment (selection bias)	Low risk	Allocation concealment performed centrally as confirmed by the authors on 3 March 2022.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Blinding was not possible for the patien s or physic ans because of the different routes of administration of the drugs under evaluation (oral vs injection); nevertheless, the principal investiga or (JG) and statisticians were blinded during statistical analysis and data valuation". Subjective outcomes reported (e.g. cancellation).
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Blinding was not possib e for the pa ients or physicians because of the different routes of administrat on of the d ugs under evaluation (oral vs injection); nevertheless, the principal i estigator (JG) and statisticians were blinded during statistical analysis and data evaluation". Subjective outcomes reported (e.g., cancellation).
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. A rition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Se ctive porting not detected.
Other bias	Low risk	Trial conducted post-2010, prospectively registered. Single centre study with plausibl recruitment rates.

Gonzalez-Gomez 2000

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Lang age:** English **Sett ng:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 90
Participants	**Inclusion criteria:** male factor requiring ICSI **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** male factor

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Gonzalez-Gomez 2000 *(Continued)*

	Subgroup (age): unstated **Subgroup (BMI):** unstated **Subgroup (ethnicity):** unstated
Interventions	**Arm 1:** long agonist plus rFSH (n = 45) **Arm 2:** long agonist plus uFSH (n = 45) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number; cancellation; follicle number; immature oocytes; total gonadotrophin dose; fertilisation rate; implantation rate; clinic l pregnancy **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** unstated **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** no cont ct detai s found **Data per participant:** yes **Calculations used to obtain ab olute event numbers:** no **Inclusion in meta-analys s:** insufficient outcome data in the abstract to include in the quantitative synthesis; author contact de ails not found

Risk of bias

Bias	Autho s' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear ris	"in a randomised manner", methodology unstated.
Allocation concealment (selection bias)	Un lear risk	Unstated.
Blinding of particip nts and personnel (p rformance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., cancellation).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., cancellation).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed. Attrition unclear.

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Gonzalez-Gomez 2000 *(Continued)*

Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	SIngle centre study. Timeline unstated. No other biases identified.

Gordon 2001

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Ireland **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 128
Participants	**Inclusion criteria:** age 20–39 years; a weight of 80%–130% of ideal body weight; normal menstrual cycle (24–35 days); ≥2-year history of infertili ith full fertility profile completed **Exclusion criteria:** endocrine abnormalit s s ch as hyperprolactinaemia and PCOS; male factor infertility **Predicted response as stated by h tria sts:** unstated **Oocyte donors:** no **Cause of infertility:** vari us **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethni ity):** no
Interventions	**Arm** long agonist plus rFSH (n = 39) **Arm 2:** long gonist plus uFSH (n = 30) **Arm 3:** long agonist plus hMG (n = 59) - two arms merged (see additional comments) **Fertil sation method:** unstated **Emb yo age at the time of transfer:** unstated **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; miscarriage; cancellation; oocyte number **Outcomes included in the meta-analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** -

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Gordon 2001 *(Continued)*

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: yes - u.d.gordon@bristol.ac.uk (16 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: Women undergoing a long downregulation pro ocol with GnRH agonist were randomised to gonadotropin drugs with varying doses of LH per ampoule recombinant FSH containing no LH (group 0, n = 39), urinary FSH (group 1, n = 30), hMG con ining 2 IU of LH per ampoule (group 25, n = 30), and hMG containing 75 IU of LH per ampoule (group 75, n = 29). Fo the purposes of meta-analysis, groups 25 and 75 were amalgamated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomized computer-g nerated code".
Allocation concealment (selection bias)	Low risk	Third-party allocation by the hospital pharmacist as confirmed with Van Wely 2011.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Single-bind study , s bjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Assessor-blind" study.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT nalysis performed. Five cycles were cancelled in goup 0; seven in group 1; nd six in total in groups 25 and 75. Attrition rate >10% in at least one trial arm.
Selective reporting (reporting bias)	Low sk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Gordts 2012

Study characteristics

Methods

Design: randomised controlled trial

Country: Belgium

Language: English

Setting: single centre

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Gordts 2012 *(Continued)*

	Recruitment period: January 2009 to July 2010
	Sample size (total randomised): 160
Participants	**Inclusion criteria:** age <40 years; first or second IVF attempt
	Exclusion criteria: ≥40 years; ≥2 failed IVF attempts; pre-implantation genetic diagnosis cycles and cycles with use of testicular sperm extraction
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 80)
	Arm 2: agonist flare plus rFSH (n = 80)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** live b rth; on o ng pr gnancy; cancellation; oocyte number; number of embryos cryopreserved
	Outcomes included in the meta-analysis: live birth
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration d te: -
	Confli t of in erest declaration: unstated
	Funding u stated
	Author correspondence: yes - sylvie.gordts@lifeleuven.be (16 September 2021)
	C culations used to obtain absolute event numbers: yes
	In lusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outc mes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Blinded envelope system".
Allocation concealment (selection bias)	Unclear risk	"Blinded envelope system".

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Gordts 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to obtain absolute event numbers from percentages. One cycle was cancelled the agonist group and six cycles were cancelled in the antagonist gro p ther fore attrition <10%.
Selective reporting (reporting bias)	Low risk	Trial conducted pre- and up to 2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre- and u to 2 10. Single centre study with plausible recruitment rates. No concerns egarding v lidity of results. Effect size difference lower than two-fold between trial ar s. No other biases detected.

Goswami 2004

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** India **Language:** English **Setting:** single centre **Recruitment perio :** Jul 2002 to August 2003 **Sample size (to al randomised):** 38
Participants	**Inclusi n cri ria:** ag ≥35 years; 1-3 failed IVF attempts due to low ovarian response to conventional long GnRH agonist stimulation protocol **Exclusion riteria:** severe endometriosis; previous pelvic surgery **Pr dicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cau e of infertility:** low ovarian reserve **bgroup (age):** yes (≥35 years) **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** letrozole plus rFSH without pituitary suppression (n = 13) **Arm 2:** long agonist plus rFSH (n = 25) **Fertilisation method:** unstated **Embryo age at the time of transfer:** cleavage stage (days 2-4)

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Goswami 2004 *(Continued)*

	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** clinical pregnancy; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbe** no **Inclusion in meta-analysis:** yes (primary analys - low risk o selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgeme t
Random sequence generation (selection bias)	Low risk	"Random-number tab es".
Allocation concealment (selection bias)	Low risk	"Sequ ntially umbered sealed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Th pe son enrolling participants, study investigators, ultrasound technicians nd clinicians were unaware of the type of protocol used".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Only the statisticians had access to the unblinded data".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised included in the analysis. One woman cancelled in each group (<10% attrition).
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010.Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Griesinger 2005

Study characteristics

Methods	**Design:** randomised controlled trial

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Griesinger 2005 *(Continued)*

	Country: Germany
	Language: English
	Setting: single centre
	Recruitment period: June 2003 to December 2003
	Sample size (total randomised): 127
Participants	**Inclusion criteria:** age 20-39 years; BMI 18-35 kg/m^2; regular menstrual cycles (24-35 days)
	Exclusion criteria: >3 previous unsuccessful ART cycles; previous poor response to gonadotrophin stimulation previous OHSS; PCOS; any other endocrine disorde no natu l uteal phase prior to treatment; abnormal uterine cavity as evaluated by ultrasonography; pr sence of a clinically significant systemic disease
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n 5)
	Arm 2: short antagonist plus rFSH & rLH (n = 62)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes repor ed:** linical pregnancy; cancellation; oocyte number
	Outcome clud d in the meta-analysis: none
Notes	**Type f pub cation:** published full-text manuscript
	Trial registr tion: unstated
	Registration date: -
	Confli t of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - georg.griesinger@frauenklinik.uni-luebeck.de (16 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of selection bias; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement

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Griesinger 2005 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Drawing sealed envelopes".
Allocation concealment (selection bias)	Unclear risk	"Drawing sealed envelopes", but unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open study", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open study", subjective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. A total of el ven cycles were cancelled in the rFSH group, and eight in the rFSH/rLH roup. ttrition >10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and publi hed pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns rega d g validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Grøndahl 2009

Study characteristics	
Methods	**Design:** randomised c trolled trial **Country:** Denmark **Language:** Engl h **Setting:** singl centre **Recruitm nt period:** unstated **Sample size (total randomised):** 30
Participants	**Incl sion criteria:** age 21-39 years; regular menstrual cycles; male factor, tubal disease, mild endometriosis or unexplained infertility **Excl sion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no

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Grøndahl 2009 *(Continued)*

Interventions	**Arm 1:** long agonist plus rFSH (n = 15) **Arm 2:** long agonist plus hMG (n = 15) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** "Supported by Hvidovre Hospital Research u dation, Hvidovre Hospital, Copenhagen University Hospital, Hvidovre, Denmark, and the Danish Research Agency." **Author correspondence:** yes - marie.groendah @hvh.regionh.dk (15 September 2021) **Calculations used to obtain absolute even numbers:** no **Inclusion in meta-analysis:** no (unclea risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	**Authors' judgement**	**S pport for judgement**
Random sequence generation (selection bias)	Unclear risk	Un tated.
Allocation concealment (selection bias)	Uncle r risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcom as-sessment (detect on bias) All outcomes	Low isk	Unstated, however only objective outcomes reported.
Incomplete outcome da (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Grøndahl 2009 *(Continued)*

Other bias	Unclear risk	Trial conducted pre-2010. Single centre study with unclear recruitment timeline. Effect size difference lower than two-fold between trial arms. No other biases detected.

Harrison 1994

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Ireland **Language:** English **Setting:** single centre **Recruitment period:** January 1992 to Novembe 1992 **Sample size (total randomised):** 150
Participants	**Inclusion criteria:** unselected women undergoing COS for ART **Exclusion criteria:** unstated **Predicted response as stated by the t alists:** unselected population **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicit):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 100) - two arms merged (see additional comments) **Arm 2:** lomi ne citr te plus hMG without pituitary suppression (n = 50) **Fertili atio method:** unstated **Embryo age the time of transfer:** unstated **Lu eal phase support:** micronised progesterone and occasionally hCG
Outcomes	**O tcomes reported:** live birth; clinical pregnancy; multiple pregnancy; miscarriage; cancellation; oocy e number **Outcomes included in the meta-analysis:** live birth; clinical pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** "Supported by Ipsen Biotech, Dublin, Ireland."

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Harrison 1994 *(Continued)*

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: "Group A received 3 mg triptorelin IM from day 1 of the cycle. Human menopausal gonadotropin 225 IU IM was given daily from downregulation. Group B was prescribed 100 mg clomifene citrate daily for 5 days from day 2 of the cycle with hMG 150 IU IM daily from day 4. Group C took buserelin acetate to downregulate at a dosage of 150 mg intranasally four times daily from day 1. Human menopausal gonadotropin 225 IU IM was given daily from when down-regulation was achieved." For the purposes of meta-analysis, groups A and C were amalgamated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated rando ation de blind to the clinicians".
Allocation concealment (selection bias)	Low risk	Central allocation by the ospital pharmacist.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Clinicians blinded, bu not patients. Subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated sub ect ve outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed, but absolute event numbers calculated based o reported percentages (e.g., live birth rates). Cycle cancellation occ rred in 15 cases in the clomifene citrate and 11 in the long agonist group. Attriti n >10% in both groups.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010.Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Haydardedeoglu 2012

Study characteri tics

Methods

Design: randomised controlled trial

Country: Turkey

Language: English

Setting: single centre

Recruitment period: March 2009 to June 2011

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Haydardedeoglu 2012 *(Continued)*

	Sample size (total randomised): 300
Participants	**Inclusion criteria:** age >23 and <35 years; PCOS; BMI >20 and <30 kg/m^2 **Exclusion criteria:** PCOS (Rotterdam criteria); hormonal treatment and oral anti-diabetics within 3 months prior to enrolment in the study **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** yes (<35 years) **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 150) **Arm 2:** short antagonist plus rFSH (n = 150) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesteron
Outcomes	**Outcomes reported:** OHSS; ongoing pr gnancy; multiple pregnancy; miscarriage; cancellation; oocyte number **Outcomes included in the met analysis:** OHSS; ongoing pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number
Notes	**Type of publication:** published f ll-text manuscript **Trial registration:** NCT0135 275 **Registration da e:** 16 2011 **Conflict of in erest declaration:** none declared **Fund g:** un tated **Author corr spondence:** none undertaken **Ca culations used to obtain absolute event numbers:** yes **Inclusi n in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Add ional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Low risk	Allocation concealment centrally managed by nurse coordinator who had no involvement in the trial.

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Haydardedeoglu 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Ten women cancelled in the long agonist group, and nineteen in the short antagonist group. Attrition >10% in at l ast o e of the trial arms.
Selective reporting (reporting bias)	High risk	Trial conducted post-2010. Retrospectively registered
Other bias	Low risk	Trial conducted pre- and p st 20 0 and etrospectively registered. Single centre study with plausible ecruitmen ates. Effect size difference lower than two-fold between trial a ms.

Hazout 1993

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** France **Language:** English **Setting:** single centre **Recruitment perio :** fou months **Sample size (to al randomised):** 182 cycles (number of women randomised unclear; some underwent more than one cycle)
Participants	**Inclu ion criteria:** age <38 years **Exclusion riteria:** age ≥38 years; infertility lasting ≥4 years; chronic oligo or anovulation; abnormal male SFA **P dicted response as stated by the trialists:** unstated **O cyte donors:** no **Cau e of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 96 cycles) **Arm 2:** agonist flare plus hMG (n = 86 cycles) **Fertilisation method:** IVF

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Hazout 1993 *(Continued)*

	Embryo age at the time of transfer: various **Luteal phase support:** hCG (plus micronised vaginal capsules where serum oestrogen was low)
Outcomes	**Outcomes reported:** cancellation **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author c tact de ils not found) **Calculations used to obtain absolute event nu bers:** no **Inclusion in meta-analysis:** no (analysis conducte per cyc e, therefore not included in the quantitative synthesis) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support f r ju gement
Random sequence generation (selection bias)	Unclear risk	"randomly assig ed", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Uns ated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unc ar risk	Data reported per cycle. Attrition unclear.
Selective reporti g (reporting bias)	Low risk	Trial conducted and published pre-2010.Selective reporting not detected.
Other bias	Low risk	Study conducted pre-2010. No concerns regarding the validity of results. Single centre study with plausible recruitment rates.

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Hedon 1988

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** France **Language:** French **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 120
Participants	**Inclusion criteria:** unstated **Exclusion criteria:** requirement of individualised COS protocol; anov lation; abnormal semen analysis **Predicted response as stated by the trialists:** un tated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus hMG (n = 60) **Arm 2:** long agonist plus hMG (n 60) **Fertilisation method:** unstated **Embryo age at the tim of transfer:** unstated **Luteal phase support:** hCG
Outcomes	**Outcomes repor ed:** oocyte number **Outcomes in uded in the meta-analysis:** none
Notes	**Type of pu lication:** published full-text manuscript **Tr al registration:** unstated **Regi tration date:** - **Con ict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not found) **Calculations used to obtain absolute event numbers:** yes **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -
Risk of bias	

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Hedon 1988 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes r ported
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. our wome were cancelled in the short protocol group, and 1 in the long rotocol (tot l = 5). Attrition <10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre 2010. Single centre study. Recruitment rates unclear as study timeline unstat d. Effect size difference lower than two-fold between trial arms. No oth r biases detected.

Hedon 1995

Study characteristics	
Methods	**Design:** randomised c ntrol ed trial **Country:** I terna onal (France and The Netherlands) **Lang age:** English **Setting:** m lticentre **Re ruitment period:** August 1992 to July 1994 **Sample size (total randomised):** 99
Participants	**Inclusion criteria:** age 18-39 years; ≤3 previous ART attempts; normal ovulatory cycles (24-35 days); good physical and mental health; body weight 80-130% of ideal body weight **Exclusion criteria:** PCOS; absence of ovarian function; infertility caused by endocrine abnormalities such as hyperprolactinaemia; contraindications for the use of GnRH agonists, FSH, hMG and/or hCG; any other ovarian and/or abdominal abnormality that would interfere with adequate ultrasound investigation; hypertension; chronic cardiovascular, hepatic, renal or pulmonary disease; male factor infertility **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various

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Hedon 1995 *(Continued)*

	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 60)
	Arm 2: long agonist plus uFSH (n = 39)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: hCG and progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; ongoing pregnancy
	Outcomes included in the meta-analysis: OHSS; cli l pregn ncy; ongoing pregnancy
Notes	**Type of publication:** published full-text manusc pt
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: "Financially supported by NV O ganon, OSS."
	Author correspondence: none undertaken (author contact details not found)
	Calculations used to obtain absolu event numbers: no
	Inclusion in meta-analysis: y s (primary analysis)
	Additional comments: -

Risk of bias

Bias	Authors' judge ent	Support for judgement
Random sequence generation (selection bias)	Low ri k	Randomisation using a randomisation list on a 3:2 ratio as confirmed by Van Wely 2011.
Allocation concealment (selection bias)	Low risk	Central allocation of a subject number in order of entrance, which corresponded to medication boxes with the medication as confirmed by Van Wely 2011.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Single-blind study", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Assessor-blind" study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Five women were did not reach oocyte retrieval in the rFSH group, and 8 in the uFSH group (total = 13). Attrition <10%.

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Hedon 1995 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Hershko Klement 2015

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Israel **Language:** English **Setting:** single centre **Recruitment period:** August 2012 to July 2013 **Sample size (total randomised):** 60
Participants	**Inclusion criteria:** unstated **Exclusion criteria:** age >37 years; o ula ion problems (WHO Class I-III); >3 previous unsuccessful IVF cycles; TESA/TESE cycles; surroga y cycles refusal to take part in the study **Predicted response as stated y the ialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI)** no **Subgroup (et nicity)** no
Interventions	**Arm 1:** s o t antagonist plus rFSH & hMG (n = 31) **Arm 2:** long agonist plus rFSH & hMG (n = 29) **Fe ilisation method:** IVF or ICSI **Em ryo age at the time of transfer:** cleavage stage (days 2-4) **Lut al phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT01419353 **Registration date:** 18 August 2011 **Conflict of interest declaration:** none declared

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Hershko Klement 2015 *(Continued)*

Funding: unstated

Author correspondence: yes - anat.clement@gmail.com (25 February 2022)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias [random sequence generation unstated]; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly chosen sealed envelope"
Allocation concealment (selection bias)	Low risk	"handled by one of the administrat rs in the clinic, who was not involved in this study".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Open trial", however only o jecti e outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Open trial", ho ever only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Four w men were not treated in the treatment group, and five in the control grou (tota = 9, attrition >10%).
Selective reporting (reporting bias)	Low risk	S udy registered prospectively and outcomes reported as per protocol.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Ho 2008

Study characteristics

Methods	**Des gn:** randomised controlled trial **Country:** Taiwan **Language:** English **Setting:** single centre **Recruitment period:** Mary 2004 to June 2006 **Sample size (total randomised):** 240

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Ho 2008 *(Continued)*

Participants	**Inclusion criteria:** age 20-39 years; good physical and mental health; regular menstrual cycles, (25-35 days); tubal, male or unexplained infertility; BMI 18-29 kg/m^2; normal uterus; bilateral ovaries; normal early follicular phase parameters **Exclusion criteria:** endometriosis stage III/IV; PCOS; >3 previously consecutive unsuccessful IVF cycles; previous low response to COS; history of recurrent miscarriage; severe OHSS in previous IVF cycles; any significant systemic disease, endocrine or metabolic abnormalities; hypersensitivity to any trial product **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus rFSH (n = 120) **Arm 2:** long agonist plus rFSH (n = 120) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavag stage (days 2-4) **Luteal phase support:** intramuscu ar p ogesterone and oral oestradiol valerate
Outcomes	**Outcomes reported:** live birth; clinic l p egnancy; ongoing pregnancy; ectopic pregnancy; cancellation; oocyte number **Outcomes included in the met -analysis:** live birth; clinical pregnancy; ongoing pregnancy; ectopic pregnancy; cancellation; oocyte number
Notes	**Type of publication** p blis ed full-text manuscript **Trial registrati :** unstated **Regist ation ate:** - **Conflict f nterest declaration:** none declared **Funding:** unstated **A hor correspondence:** none undertaken (author contact details not found) **Ca culations used to obtain absolute event numbers:** no **Incl sion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomization list".

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Ho 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	"centralized telephone procedure".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Medical staff assessing biochemical results and performing ultrasound investigation for follicle and pregnancy status were blinded to the specific group assignment of the participating patients". Unclear if patients were blinded, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Medical staff assessing biochemical results and performing ultrasound investigation for follicle and pregnancy status were linded to the specific group assignment of the participating patients". Unclear f patients were blinded, however only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and pub ished pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms No other biases detected.

Hohmann 2003

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** The Netherlands **Language:** English **Setting:** single centre **Recrui ment eriod:** November 1999 to May 2001 **Sampl siz (total randomised):** 142
Participants	**Inclusion criteria:** age 20–38 years; BMI 19–29 kg/m^2; regular menstrual cycles (25-35 days); no relev t systemic disease, severe endometriosis, uterine or ovarian abnormalities; ≤3 previous IVF cycles; and o previous IVF cycle with a low response or ovarian hyperstimulation syndrome **Excl sion criteria:** unstated **Pr dicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 45)

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Hohmann 2003 *(Continued)*

	Arm 2: short antagonist plus rFSH (n = 97) - two arms merged (see additional comments) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** various **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** ongoing pregnancy; multiple pregnancy; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** "This work was supported by the Sticht ng Voortpla tingsgeneeskunde Rotterdam and an unrestricted research grant from ASTA Medica B.V (Amsterdam, The Netherlands)." **Author correspondence:** none undertaken (author contact details not found) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear ris of se ction bias [allocation concealment unstated]; primary review outcomes not reported) **Additional comments: Women were** randomised to a GnRH agonist long protocol (group A; n = 45) or one of two GnRH antagonist proto ol commencing recombinant FSH on cycle day 2 (group B; n = 48) or cycle day 5 (group C; n = 49) For th rposes of meta-analysis, we planned to amalgamate groups B and C.

Risk of bias

Bias	Authors' judgemen	upport for judgement
Random sequence generation (selection bias)	Low risk	computer-generated randomization schedule".
Allocation concealment (selection bias)	Uncle r risk	"numbered sealed envelopes", however unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	Lo risk	Unclear, however only objective outcomes reported.
Blinding of outcome assessment (detec ion bias) All outcomes	Low risk	Unclear, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute numbers. Attrition rate >10% in at least one of the trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Hohmann 2003 *(Continued)*

Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Homburg 1990

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United Kingdom **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 46
Participants	**Inclusion criteria:** PCOS; previously failed to ovulate on several courses of clomifene citrate at a dose of 100 mg/day for 5 days **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertility:** PCOS **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** lon agon t plus hMG (n = 14) **Arm 2** long agonist plus uFSH (n = 11) **Arm 3:** hM without pituitary suppression (n = 11) **Arm 4:** uFSH without pituitary suppression (n = 10) **Fert lisation method:** unstated **Embryo age at the time of transfer:** unstated **teal phase support:** unstated
Outcomes	**Outcomes reported:** OHSS **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated

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Homburg 1990 *(Continued)*

Funding: unstated

Author correspondence: none undertaken (author contact details not found)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated", methodology uns ted.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcom s reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subje tive outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT ana ysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	T ial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Hompes 2008

Study characteristics

Methods	**Des gn:** randomised controlled trial **Country:** The Netherlands **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 629
Participants	**Inclusion criteria:** age 18-39 years; no endocrine abnormality such as PCOS, hypogonadotropic hypogonadism, or day 3 FSH levels >12 IU/l

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Hompes 2008 *(Continued)*

	Exclusion criteria: repeat ART cycles
	Predicted response as stated by the trialists: unselected population
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 312)
	Arm 2: long agonist plus rFSH (n = 317)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; ongoing pregnancy
	Outcomes included in the meta-analysis OHSS; ongoing pregnancy
Notes	**Type of publication:** published full-text manu cript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declarati n: "P.G A.H. has conducted clinical research sponsored by Abbott, Ferring, Organon, Schering, and Se ono. F.J.B. has conducted clinical research sponsored by Wyeth, Ferring, Organon, and Serono."
	Funding: "The rese rch nst utes of the participating centers were supported by Ferring BV, Hoofddorp, The Netherland "
	Author c espondence: yes - p.hompes@vumc.nl (9 January 2021)
	Calcu ations sed to obtain absolute event numbers: no
	Inclusion i meta-analysis: yes (primary analysis)
	Ad itional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random seque e genera-tion (selection bias)	Low risk	A central randomization procedure was followed by using an interactive voice response system.
Allocation concealment (selection bias)	Low risk	Central procedure using an interactive voice response system as confirmed by Van Wely 2011.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial, subjective outcomes reported.

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Hompes 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Of 293 cycles started in the HP-hMG group, only 220 had oocyte retrieval (the difference was considered the cancellation rate). Of 302 cycles started in the rFSH group, only 238 had oocyte retrieval (the difference was considered the cancellation rate). Attrition rate >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selecti e reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No conc rns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Hoomans 1999

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** International (Austria, Denmark a d he Netherlands) **Language:** English **Setting:** multicentre **Recruitment period:** October 996 to April 1998 **Sample size (total randomised):** 169
Participants	**Inclusion criteria:** age 18-39 years; BMI 18-29 kg/m^2; normal ovulatory cycles (24–35 days) **Exclusion crite :** endocrine abnormalities such as hyperprolactinaemia; PCOS; absence of ovarian func ion; 2 prev ous IVF, GIFT or ZIFT attempts with <5 oocytes retrieved; history of (within 12 months) or cu rent abuse of alcohol or drugs; investigational drug administration within 3 months prior to s reen ng; abnormal SFA **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **use of infertility:** various **Sub roup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 84) **Arm 2:** long agonist plus uFSH (n = 85) **Fertilisation method:** IVF **Embryo age at the time of transfer:** unstated

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Hoomans 1999 *(Continued)*

	Luteal phase support: variable
Outcomes	**Outcomes reported:** clinical pregnancy; miscarriage **Outcomes included in the meta-analysis:** clinical pregnancy; miscarriage
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact etails ot found) **Calculations used to obtain absolute event numbe** yes **Inclusion in meta-analysis:** yes (primary analys) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgeme t
Random sequence generation (selection bias)	Low risk	Random number table as confirmed by Van Wely 2011.
Allocation concealment (selection bias)	Low risk	Alloca on us g sealed envelopes, opaque and numbered. Only authorised access to randomised list, as per Van Wely 2011.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Ope tri l, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open trial, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but absolute event numbers calculated based on reported percentages. Four women lost between randomisation and treatment onset. No statement regarding further loss to follow-up, although only 141 women underwent ET.
Selective reporting (reporting bias)	Low isk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Hoseini 2014

Study characteristics

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Hoseini 2014 *(Continued)*

Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** June 2012 to November 2013 **Sample size (total randomised):** 50
Participants	**Inclusion criteria:** age ≤40 years; male factor, tubal factor or unexpl ined i fertility; no ovulatory dysfunction; normal baseline FSH and LH levels **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 26) **Arm 2:** short antagonist plu rFSH n 24) **Fertilisation method:** IVF or CSI **Embryo age at the time f tran fer:** N/A **Luteal phase suppo t:** N A
Outcomes	**Outcomes repo ed:** ocyte number **Outcom s i cluded in the meta-analysis:** none
Notes	**Type f pub ication:** published full-text manuscript **Trial registra ion:** IRCT2014031112307N3 **Registration date:** 21 April 2014 **Conflic of interest declaration:** none declared **Funding:** "The present study was funded by Deputy Ministry for Research, Tehran University of Medical Sciences (TUMS); grant no. 91-02-30-18324." **Author correspondence:** yes - nsalsabili56@yahoo.com (15 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias [random sequence generation unstated], high risk of other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

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Hoseini 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned by the statistician".
Allocation concealment (selection bias)	Low risk	"randomly assigned by the statistician".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed.
Selective reporting (reporting bias)	High risk	Trial conducted post 2010. Retrospectively registered.
Other bias	High risk	Trial conducted pos 2010. Retrospective registration. Single centre study with plausible recruitme t ates. Effect size difference lower than two-fold between trial arms

Hossein 2020

Study characteristics	
Methods	**Design:** randomised c ntrol ed trial **Country:** I an **Lang age:** English **Setting:** s gle centre **Re ruitment period:** September 2018 to October 2019 **Sample size (total randomised):** 200
Participants	**Inclusion criteria:** age <40 years; AMH >1.5 ng/ml; BMI <30 kg/m^2; presence of both ovaries; AFC >5-7 **Exclusion criteria:** smoking; uterine anomalies; adrenal insufficiency; uncontrolled thyroid disease; endometriosis stage ≥3; hyperprolactinaemia; neoplastic ovarian disorders; repeated implantation failure; severe male factor **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2)

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Hossein 2020 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** progestogen plus hMG (n = 100) **Arm 2:** short antagonist plus hMG (n = 100) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** freeze-all policy
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; miscarriage; cancellation; ocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** IRCT20181031041519N2 **Registration date:** 10 June 2019 **Conflict of interest declaration:** none declared **Funding:** "The study was supported by Vice-Chancellor for Research and Technology of Tehran University of Medical Sciences, Tehran, Iran." **Author correspondence:** yes - dr_ghazi82@yahoo.com (16 September 2021) **Calculations used to obtain absolute vent numbers:** no **Inclusion in meta-analysis** yes (s n itivit analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgemen	Support for judgement
Random sequence generation (selection bias)	Unclear ri k	Unstated.
Allocation concealment (selection bias)	Unclear r	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	U clear risk	"Infertility clinician (…) blind to the allocation", however unclear if patients were blinded. Subjective outcomes reported.
Blinding of outc me as sessment (detecti n bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Three patients in the dydrogesterone group and five in the antagonist group were cancelled. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Retrospectively registered. Selective reporting not detected.

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Hossein 2020 *(Continued)*

Other bias	High risk	Trial conducted post-2010 and retrospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Hosseini 2010

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** 2006 **Sample size (total randomised):** 112
Participants	**Inclusion criteria:** age <35 years; BMI <27 kg/m^2; PCOS; normal prolactin and thyroid hormone levels; normal SFA **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** yes (<35 years) **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** lo g gonis plus rFSH & hMG (n = 55) **Arm** short ntagonist plus rFSH & hMG (n = 57) **Fertilisati method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Lute l phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; multiple pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - mahdavi_a@tums.ac.ir (15 September 2021)

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Hosseini 2010 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization and group assignments were pe formed in sequentially numbered PCOS patients."
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes re orted
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis perform No loss to follow-up.
Selective reporting (reporting bias)	Low risk	ITT erformed. No loss to follow-up.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Hsieh 2008

Study characteristics

Methods	**D sign:** randomised controlled trial **Country:** Taiwan **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 251
Participants	**Inclusion criteria:** age 18-39 years; body weight 40-70 kg **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated

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Hsieh 2008 *(Continued)*

	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 144) - three arms merged (see additional comments)
	Arm 2: long agonist plus rFSH (n = 107) - two arms merged (see additional comments)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-)
	Luteal phase support: hCG and progesterone
Outcomes	**Outcomes reported:** OHSS; miscarriage; oocyte umber
	Outcomes included in the meta-analysis: OHSS
Notes	**Type of publication:** published full-text man script
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: nstated
	Funding: unstated
	Author correspondence: yes hongt 2000@yahoo.com.tw (23 February 2022)
	Calculations used to obtain abs lute event numbers: no
	Inclusion in meta-analysis yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth nd/or OHSS])
	Additional comments: Women undergoing in vitro fertilisation/intracytoplasmic sperm injection and embryo trans r were divided into five groups: (1) cetrorelix 0.25 mg (n = 86); (2) cetrorelix 0.2 mg (n = 28); (cetror lix 0.15 mg (n = 30); (4) leuprolide acetate (LA) 0.5 mg/day (n = 58); (5) single half-dose LA depot 1 88 mg (n = 49). For the purposes of meta-analysis, groups 1-3 and groups 4-5 were merged.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera tion (selection bias	Uncl ar risk	Unstated.
Allocation concealme t (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (perfor- mance bias) All outcomes	High risk	"open-label", sujective outcomes reported (e.g., OHSS).
Blinding of outcome as- sessment (detection bias)	High risk	"open-label", sujective outcomes reported (e.g., OHSS).

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Hsieh 2008 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis not strictly reported, however possible to extract absolute event rates. Attrition unstated.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	High risk	Trial conducted pre-2008. Single-centre study with unclear recruitment rates. Uneven distribution of patient numbers across all five groups, ranging between 28-86 participants per group. Randomisation ratio unclear.

Hugues 2001

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** France **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 88
Participants	**Inclusion criteria:** age 18-38 years; serum FSH 5-12 IU/l **Exclusion criteria:** single ovary; ovarian endometriosis **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus uFSH (n = 32) **Arm 2:** agonist flare plus rFSH (n = 56) - two arms merged (see additional comments) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** unstated **Luteal phase support:** micronised progesterone (route unstated)
Outcomes	**Outcomes reported:** ongoing pregnancy; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript

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Hugues 2001 *(Continued)*

Trial registration: unstated

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: yes - jean-noel.hugues@jvr.ap-hop-paris.fr (16 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection and other biases primary review outcomes not reported)

Additional comments: A total of 88 women undergoing IVF-ET with short ag nist protocol were randomised to receive uFSH (150 IU/day, n = 32), follitropin-α (10 IU/day, n = 28), or follitropin-β (100 IU/day, n = 28). For the purposes of meta-analysis, w planned to amalgamate women in the follitropin alpha and beta groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"list of random numb rs".
Allocation concealment (selection bias)	Unclear risk	"concealed meth d - nvelope", although unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"not blind d , however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	ot blinded", however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclea risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Huirne 2006

Study characteristics

Methods	**Design:** randomised controlled trial
	Country: International (Austria, Belgium, France and The Netherlands)
	Language: English

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Huirne 2006 *(Continued)*

	Setting: multicentre
	Recruitment period: unstated
	Sample size (total randomised): 182
Participants	**Inclusion criteria:** age 18-39 years; normal SFA
	Exclusion criteria: previous ART cycles where <3 oocytes were collected; >2 previous ART cycles without achieving a clinical pregnancy; contraindications to ART; systemic disease
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 91)
	Arm 2: short antagonist plus rFSH (n = 91)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: various
	Luteal phase support: vaginal pr ge tero e
Outcomes	**Outcomes reported:** live bir h; OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; ectopic pregnancy; cancellation; oocy e number; number of embryos cryopreserved
	Outcomes included in the meta analysis: live birth; OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; ectopic preg ancy; cancellation; oocyte number; number of embryos cryopreserved
Notes	**Type of publicat on:** publi hed full-text manuscript
	Trial re str tion: nstated
	Regi ration date: -
	Conflict of i terest declaration: unstated
	Funding: "Supported by Serono."
	Autho correspondence: yes - cb.lambalk@vumc.nl (16 September 2021)
	Calc lations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated concealed randomization list".

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Huirne 2006 *(Continued)*

Allocation concealment (selection bias)	Low risk	"computer-generated concealed randomization list".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Seven women we e cancelled in the long agonist group and six in the short antagonist arm.
Selective reporting (reporting bias)	Low risk	Trial conducted and published p 2010 Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicent e study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Humaidan 2004

Study characteristics	
Methods	**Design:** randomised controll d trial **Country:** Denmark **Language:** English **Setting:** single centr **Recruitm t peri d:** November 2001 to October 2002 **Samp e size otal randomised):** 231
Participants	**Inclusion cr teria:** age <40 years; baseline FSH <10 IU/l; menstrual cycles between 25 and 34 days **Exclusion criteria:** unstated **Predi ted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** yes (<35 years and ≥35 years) **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 116) **Arm 2:** long agonist plus rFSH (n = 115) **Fertilisation method:** IVF or ICSI

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Humaidan 2004 *(Continued)*

	Embryo age at the time of transfer: various
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; miscarriage; oocyte number
	Outcomes included in the meta-analysis: clinical pregnancy; miscarriage; oocyte number
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none undertaken
	Calculations used to obtain absolute event nu bers: no
	Inclusion in meta-analysis: yes (primary analysis ow risk of selection and other biases)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgeme t
Random sequence generation (selection bias)	Low risk	"computer genera ed random numbers".
Allocation concealment (selection bias)	Low risk	"sealed, unlabelled envelopes, each containing a unique study number", cen- lly m naged by a nurse.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Non-assessor blind", only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low sk	"Non-assessor blind", only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Humaidan 2017

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** International (eighteen European countries) **Language:** English **Setting:** multicentre **Recruitment period:** January 2014 to February 2015 **Sample size (total randomised):** 939
Participants	**Inclusion criteria:** age ≥18 to <41 years; BMI 18-31 kg/m² (inclusive); eligible f r COS and ART treatment (including ICSI); diagnosis of low ovarian response (Bo ogna criteria) **Exclusion criteria:** other 'risk factors for low ovarian r sponse , at least two previous episodes of POR after maximal stimulation; POI; use of PGS/D **Predicted response as stated by the trialists:** p edicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** yes (<35 years and ≥35 years) **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 462) **Arm 2:** long agonist plus rFSH (n = 477) **Fertilisation method** IVF or ICSI **Embryo age at the me of t ansfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outc mes reported:** live birth; clinical pregnancy; ongoing pregnancy; miscarriage; ectopic pregnancy; canc lla ion; oocyte number **Outcomes included in the meta-analysis:** live birth; clinical pregnancy; ongoing pregnancy; miscarriage; ectopic pregnancy; cancellation; oocyte number
Notes	**Type o publication:** published full-text manuscript **Tria registration:** NCT02047227 **Registration date:** 28 January 2014 **Conflict of interest declaration:** "P.H. has received honoraria for lectures and unrestricted research grants from Ferring, Merck KGaA and MSD. D.R. is a former employee of EMD Serono, a business of Merck KGaA, Darmstadt, Germany. J.S., J.H. and W.C. are employees of EMD Serono Research and Development Institute, a business of Merck KGaA, Darmstadt, Germany. T.D.'H. and S.L. are employees of Merck KGaA, Darmstadt, Germany." **Funding:** "This study was funded by Merck KGaA, Darmstadt, Germany" **Author correspondence:** yes - peter.humaidan@midt.rm.dk (9 February 2021)

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Humaidan 2017 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Women were randomized via an interactive vo ce response system".
Allocation concealment (selection bias)	Low risk	"Blinded treatment allocation".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel were blinded but not women. Subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis followed Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial c nduc ed post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.
Other bias	Low risk	T ial conducted post-2010 and prospectively registered. Multicentre study. Effect size difference lower than two-fold between trial arms.

Hwang 2004

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Taiwan **L nguage:** English **Sett ng:** single centre **Recruitment period:** January to December 2003 **Sample size (total randomised):** 56
Participants	**Inclusion criteria:** PCOS **Exclusion criteria:** age >38 years; serum FSH >12 mIU/ml; adrenal hyperplasia; Cushing syndrome; androgen-producing tumours; hyperprolactinaemia; thyroid dysfunction **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no

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Hwang 2004 *(Continued)*

	Cause of infertility: PCOS
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus hMG (n = 27)
	Arm 2: long agonist plus hMG (n = 29)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; ongoing pregnancy; mis iage; c ncellation; oocyte number
	Outcomes included in the meta-analysis: OHSS ongoing pr gnancy; miscarriage; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: un t ted
	Funding: unstated
	Author correspondence: ye - m0 1015@ms.skh.org.tw (16 September 2021)
	Calculations used to obtain ab olute event numbers: yes
	Inclusion in meta-analys s: yes (primary analysis - low risk of selection and other biases)
	Additional commen s -

Risk of bias

Bias	Auth rs' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated block randomization numbers".
Allocation concealment (selection bias)	Low ri k	"opening sealed envelopes containing computer-generated block randomization numbers".
Blinding of partic pants and personnel (erformance bias) All outcomes	U clear risk	The laboratory staff were blinded to the stimulation protocol. Unclear if patients and clinicians blinded, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, subjective outcomes reported (OHSS, cancellation rate).
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers from percentages for some outcomes (e.g. OHSS). Two women discon-

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Hwang 2004 *(Continued)*

		tinued the intervention in the antagonist group and five women in the agonist group. Attrition >10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Ibrahim 2011

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Egypt **Language:** English **Setting:** single centre **Recruitment period:** December 2006 to M y 200 **Sample size (total randomised):** 59
Participants	**Inclusion criteria:** ovarian volum <3 ml, AFC <6, FSH >8 IU/l **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility** low ova ian reserve **Subgroup (age)** no **Subgro p (B I):** no **Subgr up (thnicity):** no
Interventions	**Arm 1:** agonist flare plus hMG (n = 30) **A m 2:** short antagonist plus hMG (n = 29) **Fe tilisation method:** IVF or ICSI **Emb yo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** ongoing pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** -

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Ibrahim 2011 *(Continued)*

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: yes - zakiamahdyabolill@yahoo.com (16 September 2021)

Calculations used to obtain absolute event numbers: yes

Inclusion in meta-analysis: no (unclear risk of selection bias; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind" trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double blind" trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysi not strictly performed but possible to extract event numbers from percentages for some of the outcomes (e.g., cancellation rates). Six women ca celled in the agonist protocol and five in the short antagonist protocol. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Tria conducted pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Ilhana 2014

Study characteristi s

Methods

Design: randomised controlled trial

Country: Turkey

Language: English

Setting: single centre

Recruitment period: November 2008 to February 2010

Sample size (total randomised): 70

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Ilhana 2014 *(Continued)*

Participants	**Inclusion criteria:** age 25-35 years; BMI 18-29 kg/m^2; mild male factor, tubal factor or unexplained infertility **Exclusion criteria:** age >35 years; PCOS; predicted low response (<4 follicles <15 mm or previous cycle cancellations); previous fertilisation failure; systemic, endocrine or metabolic illnesses; diminished ovarian reserve **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 23) **Arm 2:** long agonist plus rFSH & hMG (n = 47) - two rms merged (see additional comments) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage s age (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** clinical preg ancy; oocyte number; number of cleavage-stage embryos **Outcomes included in the meta-an lysi :** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** ACTRN126110 1133921 **Registration date:** 1 October 2011 **Conflict of interest decl ration:** unstated **Funding:** uns ated **Autho correspondence:** yes - gokceanik@yahoo.com (16 September 2021) **Calculations sed to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias; primary review outcomes not reported) **Additio al comments:** seventy women were randomised to undergo a long GnRH agonist plus rFSH prot col (n = 23) or a long GnRH agonist protocol using rFSH and hMG from the onset or stimulation (n = 23) or rFSH and hMG from when a leading follicle measured 10 mm (n = 23)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.

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Ilhana 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted pre- and up to 2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre- and u to 2 10. Single centre study with plausible recruitment rates. No concerns egarding v lidity of results. Effect size difference lower than two-fold between trial ar s. No other biases detected.

Imoedemhe 1998

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Saudi Arabia **Language:** English **Setting:** single centre **Recruitment perio :** un tated **Sample size (to al randomised):** 114
Participants	**Inclusi n cri ria:** PCOS **Exclus n c iteria:** unstated **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **C use of infertility:** PCOS **Sub roup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** uFSH without pituitary suppression (n = 57) **Arm 2:** long GnRH agonist plus uFSH (n = 57) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** unstated

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Imoedemhe 1998 *(Continued)*

	Luteal phase support: unstated
Outcomes	**Outcomes reported:** total dose of gonadotrophin; duration of stimulation; oocyte number; fertilisation rate; embryo number; clinical pregnancy; OHSS; miscarriage **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analy is - includi g all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** no author contact de ails found

Risk of bias

Bias	Authors' judgement	Support for judgeme t
Random sequence generation (selection bias)	Unclear risk	Unstated
Allocation concealment (selection bias)	Unclear risk	Unsta d.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Uns ated, subjective outcomes reported (e.g., OHSS).
Blinding of outcome assessment (detection bias) All outcomes	Uncl r risk	Unstated, subjective outcomes reported (e.g., OHSS).
Incomplete outcome data (attrition bias) All outcomes	U clear risk	Unclear whether ITT analysis performed. Attrition unclear.
Selective reportin (reporting bias)	Unclear risk	Selective reporting not detected.
Other bias	Unclear risk	Single centre study conducted pre-2010. Timeline unstated.

IRCT20200328046881N1 2020

Study characteristics

Methods	**Design:** randomised controlled trial

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IRCT20200328046881N1 2020 *(Continued)*

	Country: Iran
	Language: English
	Setting: single centre
	Recruitment period: May 2020 to May 2021
	Sample size (total randomised): 216
Participants	**Inclusion criteria:** women aged <40 years
	Exclusion criteria: cancer; stimulation protocol other than short GnRH antagonist
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus letrozole & rFSH & hMG (n = 104)
	Arm 2: short antagonist plus rFSH & hMG (n = 112)
	Fertilisation method: ICSI
	Embryo age at the time of transfe unst ted
	Luteal phase support: vagin l and tramuscular progesterone
Outcomes	**Outcomes reported:** clinical p nancy; miscarriage; ectopic pregnancy; cancellation; oocyte number; number of embryos c yop eserved
	Outcomes included in the meta-analysis: clinical pregnancy; miscarriage; ectopic pregnancy; cancellation; oocyte number; number of embryos cryopreserved
Notes	**Type o publi ation:** t ial registration record, correspondence with the authors
	Trial reg st ation: IRCT20200328046881N1
	Registration date: 5 April 2020
	C flict of interest declaration: unstated
	Fu ding: unstated
	Author correspondence: yes - mahbandarianmd@yahoo.com (16 September 2021) yielded the results included in the meta-analysis
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement

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IRCT20200328046881N1 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	"random permuted block (block randomization)".
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded, but not personnel. Only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Two women were cancelled in the placebo group. Attrition <10% in both study a ms.
Selective reporting (reporting bias)	Low risk	Selective reporting not de cted.
Other bias	Low risk	Study conducted post-2010 and prospectively registered. Single centre study with plausible rec u tme t rates. No evidence of other biases.

Jansen 1998

Study characteristics	
Methods	**Design:** randomised control d t ial **Country:** The Nethe lands **Language:** Engli h **Setting:** sing e cen e **Recr tment period:** March 1992 to February 1994 **Sample siz (total randomised):** 109
Participants	**Inclusion criteria:** age 18-39 years; ≤3 previous ART cycles with collected oocytes; normal ovulatory cycles (24-35 days); body weight 80-130% of the ideal body weight **Excl sion criteria:** infertility caused by endocrine abnormalities such as hyperprolactinaemia, PCOS and bsence of ovarian function; any ovarian and/or abdominal abnormality interfering with adequate ultrasound investigation; hypertension; chronic cardiovascular, hepatic, renal or pulmonary disease; a history of (within 12 months) or current abuse of alcohol or drugs; administration of non-registered investigational drugs within 3 months prior to screening; male infertility **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no

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Jansen 1998 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** rFSH without pituitary suppression (n = 54) **Arm 2:** hMG without pituitary suppression (n = 35) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** hCG or progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; ongoing pregnancy oocyt number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertake (uthor contact details not found) **Calculations used to obtain absolute ev nt numbers:** no **Inclusion in meta-analysis:** yes (sensit vity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS] **Additional comments:** -

Risk of bias

Bias	**Authors' judgemen**	**upport for judgement**
Random sequence generation (selection bias)	Low risk	randomization list".
Allocation concealment (selection bias)	Uncl r risk	"randomization list corresponding with patient boxes in which the medication was kept".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unclear, however only objective outcomes reported.
Blinding of outcome assessment (detec ion bias) All outcomes	Low risk	"assessor-blind" trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not performed due to study ending prematurely, but possible to extract absolute event numbers. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Study ended prematurely, thus not all women randomised received treatment. Trial conducted and published pre-2010. No evidence of selective reporting.

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Jansen 1998 *(Continued)*

Other bias	High risk	Study ended prematurely "due to non-medical factors outside our control". Effect size difference lower than two-fold between trial arms.

Kahn 1999

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** The Netherlands **Language:** English **Setting:** single centre **Recruitment period:** April 1992 to April 1994 **Sample size (total randomised):** 146
Participants	**Inclusion criteria:** age 18-39 years; ≤3 previous IVF cycles; ovulatory menstrual cycles; good physical and metal health; body weight 80-130% of ideal body weight **Exclusion criteria:** endocrine abnormaliti s; PCOS; hyperprolactinaemia; absence of ovarian function; any ovarian and abdominal abnormality tha could interfere with adequate ultrasound examination; hypertension or any cardiovascular, hepa ic renal or pulmonary disease; alcohol or drug abuse; male infertility (concentration <10 x 10^6/ml a d <40% motility and <40% normal morphology) **Predicted response as stated by h tria sts:** unstated **Oocyte donors:** no **Cause of infertility:** vari us **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethni ity):** no
Interventions	**Arm** long agonist plus rFSH (n = 86) **Arm 2:** long gonist plus uFSH (n = 60) **Fe tilisation method:** IVF **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Lute l phase support:** intramuscular and vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; cancellation; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated

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Kahn 1999 *(Continued)*

Funding: unstated

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The included patients were given a umber when they were eligible which corresponded to a list and a box of medication".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcom s reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"assessor-blind tudy"
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT ana ysis performed. Total attrition (withdrawals and cancellations) in the rFSH group 19, and in the uFSH group = 15. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	T ial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Kahraman 2005

Study characteristics

Methods	**Des gn:** randomised controlled trial **Country:** Turkey **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 22
Participants	**Inclusion criteria:** low response - unspecified

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Kahraman 2005 *(Continued)*

	Exclusion criteria: unstated
	Predicted response as stated by the trialists: predicted low response
	Oocyte donors: no
	Cause of infertility: low ovarian reserve
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus letrozole & rFSH (n = 12)
	Arm 2: agonist flare plus rFSH (n = 10)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** cancellation; oocyte number
	Outcomes included in the meta-analysis none
Notes	**Type of publication:** conference abstrac
	Trial registration: unstated
	Registration date: -
	Conflict of interest declarati n: uns ated
	Funding: unstated
	Author correspond nce: ye - korhankahraman@hotmail.com (9 February 2021)
	Calculations us d to o in absolute event numbers: no
	Inclusion in eta-a alysis: no (unclear risk of selection bias; primary review outcomes not reported)
	Addit nal omments: -

Risk of bias

Bias	Au hors' judgement	Support for judgement
Random sequence genera tion (selection bias)	Unc ear risk	"subjects randomized into two groups".
Allocation conc alment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (perfor-mance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., cancellation).
Blinding of outcome as-sessment (detection bias)	Unclear risk	Unstated, subjective outcomes reported (e.g., cancellation).

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Kahraman 2005 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Two cycles cancelled in group A, and three in group B. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect ize difference lower than two-fold between trial arms. No other biases detected.

Kahraman 2009

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Turkey **Language:** English **Setting:** single centre **Recruitment period:** November 2003 t April 2007 **Sample size (total random sed):** 42
Participants	**Inclusion criteria:** low respo se def ed when one or more of the following criteria were present in at least one previous failed ART cycle (using a standard GnRH agonist long protocol): number of mature oocytes retrieved <4; serum o t diol level <500 pg/ml on the day of hCG administration; or a previous cancelled stimulation cycle due to low ovarian response **Exclusion criteria:** PCOS; se ere endometriosis (according to the revised American Fertility Society stage III and IV); presenc of only one ovary **Predict d re ponse s stated by the trialists:** predicted low response **Oocyt don rs:** no **Cause of infe tility:** various **Subgroup (age):** no **bgro p (BMI):** no **Sub roup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus rFSH (n = 21) **Arm 2:** short antagonist plus rFSH (n = 21) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number

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Kahraman 2009 *(Continued)*

	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - korhankahraman@hotmail.com (15 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation based on the consecutive number method."
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, ubject ve outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Attrition <10% in both study arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Karimzadeh 2010

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English

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Karimzadeh 2010 *(Continued)*

	Setting: single centre
	Recruitment period: January 2008 to December 2008
	Sample size (total randomised): 243
Participants	**Inclusion criteria:** age 18–35 years; BMI 18-30 kg/m^2; regular and proven ovulatory menstruation cycle (26-35 days); basal FSH <10 IU/l; first IVF cycle; unexplained infertility, male factor, tubal factor, early stage endometriosis and cervical factor
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: predicted normal response
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 122)
	Arm 2: short antagonist plus clomifene ci ate & rFSH & hMG (n = 121)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transf r: cleavage stage (days 2-4)
	Luteal phase support: intramuscula progesterone
Outcomes	**Outcomes reported:** OHSS; cl nical pregnancy; ongoing pregnancy; cancellation; oocyte number
	Outcomes included in the meta analysis: OHSS
Notes	**Type of publication** p blis ed full-text manuscript
	Trial registrati : unstated
	Regist ation ate: -
	Conflict f nterest declaration: unstated
	Funding: unstated
	Au hor correspondence: yes - prof_karimzade@yahoo.com (16 September 2021)
	Ca ulations used to obtain absolute event numbers: yes
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization schedule".

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Karimzadeh 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	"numbered sealed envelopes", although unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Absolute values calculated from percenta es for some outcomes (e.g. clinical pregnancy rate). ITT analysis not strictly p rforme but possible to extract absolute numbers. Sixteen women were lo t to follow-up and two did not undergo embryo transfer in group A a d nineteen were lost to follow-up and four cancelled in group B. Attritio 0% in oth trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-201 . Selective r porting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between tria a ms. No other biases detected.

Khalaf 2010

Study characteristics	
Methods	**Design:** randomised contr lled t ial **Country:** France **Language:** Engli h **Setting:** ingle cen re **Recr itment period:** unstated **Sample siz (total randomised):** 50
Participants	**Inclusion criteria:** age ≤35 years; BMI 18-24 kg/m^2; regular menstrual cycles; normal basal serum FSH (≤10 U/l), LH (≤10 IU/l) and oestradiol ≤50 pg/ml **Excl sion criteria:** endometriosis; PCOS; previous OHSS **Pr dicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus rFSH (n = 28)

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Khalaf 2010 *(Continued)*

	Arm 2: short antagonist plus rFSH (n = 22) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** N/A **Luteal phase support:** N/A
Outcomes	**Outcomes reported:** review outcomes not reported **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** "This work was supported by Program e Hospitali r de Recherche Clinique (PHRC 02/059), France." **Author correspondence: yes -** benhaim-a@chu-caen.fr (23 February 2022) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (review out omes ot reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support fo judgement
Random sequence generation (selection bias)	Unclear risk	"Pati t were randomly assigned, without blinding, by balloting during the clinician's consultation".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low ri k	No blinding undertaken. Only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding undertaken. Only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	U clear risk	ITT analysis reported. Attrition unstated.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study with unclear recruitment timeline.

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Kilani 2003

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** International (Italy and Jordan) **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 100
Participants	**Inclusion criteria:** regular menstrual cycles (25-35 days); BM 18-27 kg/m^2; pelvic ultrasound showing a uterus and ovaries of normal size and structure (no signs o PCOS); normal baseline biochemical and endocrine determi ns; reproductive hormones within the normal range for the early/mid-follicular phase of the cyc e; no histo y or signs of endometriosis; ≤3 previous IVF/ICSI cycles; no hormone therapy within the p evious three months **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 50) **Arm 2:** long agonist plu hMG (n = 50) **Fertilisation me hod:** ICSI **Embry age a the time of transfer:** cleavage stage (days 2-4) **Luteal pha e support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; moderate OHSS; multiple pregnancy; miscarriage; oocyte number **Ou comes included in the meta-analysis:** live birth
Notes	**Typ of publication:** published full-text manuscript **T al registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** "Supported in part by a grant from Ferring Pharmaceuticals A/S, Copenhagen." **Author correspondence:** yes - marco.filicori@unibo.it (16 September 2021) **Calculations used to obtain absolute event numbers:** no

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Kilani 2003 *(Continued)*

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation performed centrally, but no details of methodology.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and physicians aware of th treatm nt allocation, whereas ultrasound personnel and laboratory pers nnel were not. Subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patients and physicians aw re of the treatment allocation, whereas ultrasound personnel and laboratory personnel were not. Subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed S ven women were cancelled in the rFSH group, and six in the hMG group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conduc ed p e-2010. Registration unstated. Selective reporting not detected
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between tri- l arms. No other biases detected.

Kim 2011

Study characteristics

Methods	**Design:** randomised controlled trial **C untry:** South Korea **La guage:** English **Sett ng:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 120
Participants	**Inclusion criteria:** age 28-41 years; BMI 19-30 kg/m^2; low-responding women defined as repeated day 3 levels of FSH >8.5 mIU/ml, and/or AFC ≤5 **Exclusion criteria:** fertility treatment within the preceding three months; PCOS **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no

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Kim 2011 *(Continued)*

	Cause of infertility: low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 80) - two arms merged (see additional comments) **Arm 2:** long agonist plus rFSH (n = 40) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; m l iple pre nancy; miscarriage; cancellation; oocyte number; number of embryos cryopreserve **Outcomes included in the meta-analysis:** live b th
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** ye - chnkim@amc.seoul.kr (16 September 2021) **Calculations used to obtain ab olute event numbers:** no **Inclusion in meta-analys s:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** study comparing GnRH antagonist multiple-dose protocol with (Group A, n = 40) or with ut OCP (Group B, n = 40) pretreatment, compared with a GnRH agonist low-dose long protocol (Group C n = 40) n low-responding women. For the purposes of meta-analysis, we amalgamated groups A and B.

Risk of bias

Bias	Au hors' judgement	Support for judgement
Random sequence genera tion (selection bias)	Low risk	"computer-generated list".
Allocation concealmen (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (perfor-mance bias) All outcomes	Unclear risk	Unstated, subjective outcomes (e.g., cancellation) reported.
Blinding of outcome as-sessment (detection bias)	Unclear risk	Unstated, subjective outcomes (e.g., cancellation) reported.

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Kim 2011 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Attrition <10% in all three groups.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Unclear registration status. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Kim 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** South Korea **Language:** English **Setting:** single centre **Recruitment period:** January 2003 to March 2008 **Sample size (total randomised):** 21
Participants	**Inclusion criteria:** age 25-39 years; PCOS (Rotterdam criteria); good health with normal cardiac, hepatic and renal functions; spontaneous onset of puberty and normal sexual development; no hormonal therapy within the preceding three months **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertility:** PCOS **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 106) **Arm 2:** long agonist plus rFSH (n = 105) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; severe OHSS; clinical pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number; number of embryos cryopreserved

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Kim 2012 *(Continued)*

	Outcomes included in the meta-analysis: live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - chnkim@amc.seoul.kr (16 September 2021 **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - includi g al studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated li t".
Allocation concealment (selection bias)	Unclear risk	"sealed env l pes", although unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated however only objective outcomes reported for the purposes of meta analy is.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Uns ated, however only objective outcomes reported for the purposes of me a-analysis.
Incomplete outcome data (attrition bias) All outcomes	Low ri k	ITT analysis not strictly performed but possible to extract absolute values. One cycle in the antagonist group and two in the agonist group were cancelled after oocyte retrieval due to high risk of OHSS. Attrition <10% in both arms.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Unclear registration status. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Kingsland 1992

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** United Kingdom

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Kingsland 1992 *(Continued)*

	Language: English
	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 308
Participants	**Inclusion criteria:** first ART cycle
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** hMG without pituitary suppression (n = 81)
	Arm 2: clomifene citrate plus hMG without pituit ry suppression (n = 77)
	Arm 3: agonist flare plus hMG (n = 74)
	Arm 4: long agonist plus hMG (n = 76)
	Fertilisation method: unstated
	Embryo age at the time of t nsfer cleavage stage (days 2-4)
	Luteal phase support: hCG
Outcomes	**Outcomes reporte :** liv bi h; miscarriage; ectopic pregnancy; cancellation; oocyte number; number of cleavage-stage emb yos
	Outcomes includ d in the meta-analysis: live birth
Notes	**Type of publ cation:** published full-text manuscript
	Trial regist ation: unstated
	Registration date: -
	Conf ct of interest declaration: unstated
	Fun ing: unstated
	Author correspondence: yes - charles.kingsland@carefertility.com (16 September 2021)
	Calculations used to obtain absolute event numbers: yes
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement

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Kingsland 1992 *(Continued)*

Random sequence generation (selection bias)	Low risk	"drawing serially numbered sealed envelopes (…) allocated by reference to random tables".
Allocation concealment (selection bias)	Low risk	"serially numbered sealed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Absolute values calculated from pe entages for some outcomes (e.g. live birth rate). ITT analysis not tric perfo med but possible to extract absolute numbers. Eleven women were canc lled in the hMG-only group; seven in the clomifene citrate and hMG group; eig t in the GnRH agonist flare and hMG group; and nine in the lon GnRH agonist group. Attrition >10% in groups A and D.
Selective reporting (reporting bias)	Low risk	Trial conducted and p blished pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre 2 10. Single centre study. Recruitment rates unclear as study time ine nstated. Effect size difference lower than two-fold between trial arms. No other iases detected.

Koichi 2006

Study characteristics	
Methods	**Design:** random sed controlled trial **Countr :** Jap n **Langu ge:** nglish **Setting:** singl centre **Recruitment period:** January to September 2004 **mple size (total randomised):** 192
Participants	**Incl sion criteria:** age <40 years; BMI <27 kg/m^2 **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2)

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Koichi 2006 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus uFSH (n = 66) **Arm 2:** short antagonist plus uFSH (n = 63) **Arm 3:** short antagonist plus uFSH & uhCG (n = 63) **Fertilisation method:** unstated **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** oral oestradiol and vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; miscarriage; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscrip **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - info@ivfky no or.jp (23 February 2022) **Calculations used to obtain abso ute event numbers:** no **Inclusion in meta-analysis:** yes (sen itiv ty analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	**Authors' judgement**	**S pport for judgement**
Random sequence generation (selection bias)	Unclea risk	"selection of sealed envelopes".
Allocation concealment (selection bias)	Unclear risk	"selection of sealed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Unc ar risk	Unstated, subjective outcomes reported (e.g., OHSS).
Blinding of outco e assessment (detection ias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., OHSS).
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis reported. Attrition rate >10% in the long agonist protocol.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.

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Koichi 2006 *(Continued)*

Other bias	Low risk	Single centre study with plausible recruitment rates, conducted pre-2010.

Konig 2013

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** International (Belgium and The Netherlands) **Language:** English **Setting:** multicentre **Recruitment period:** January 2004 to September 2010 **Sample size (total randomised):** 253
Participants	**Inclusion criteria:** age 35-43 years; regular cycles (5-35 day) **Exclusion criteria:** previous high response to COS; PCOS; stage III-IV endometriosis **Predicted response as stated by the trialists:** nstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist lus rFSH & rLH (n = 125) **Arm 2:** short ant gonis lus rFSH (n = 128) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phas support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; multiple pregnancy; miscarriage; ectopic pregnancy; cancellatio oocyte number; number of embryos cryopreserved **Out omes included in the meta-analysis:** clinical pregnancy; multiple pregnancy; miscarriage; ectopi pregnancy; cancellation; oocyte number; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript **Trial registration:** ISRCTN10841210 **Registration date:** 14 February 2006 **Conflict of interest declaration:** none declared **Funding:** "Supported by the Foundation for Gynecological Research and Education, Amsterdam, The Netherlands. The funding sources did not influence the design, collection, management, analysis or interpretation of the study."

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Konig 2013 *(Continued)*

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random permutation table".
Allocation concealment (selection bias)	Low risk	"Serially numbered, opaque, sealed envel pes".
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open label for patients nd doctor ", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open label for patien s and doctors", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis pe formed. Nine women cancelled in the rFSH/rLH group, and fifteen in th rF H-o ly group. Attrition >10-% in the latter.
Selective reporting (reporting bias)	Low risk	Trial onduc ed pre- and up to 2010. Registered in 2006.
Other bias	Low risk	T ial conducted pre- and up to 2010. Multicentre study. No concerns regarding alidity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Kovacs 2010

Study characteristics

Methods	**Design:** randomised controlled trial **Cou try:** Hungary **L nguage:** English **Setting**: single centre **Recruitment period:** 9 months **Sample size (total randomised):** 50
Participants	**Inclusion criteria:** age ≤40 years; normal baseline FSH (<10 IU/l); first or second IVf attempt; treatment using own gametes **Exclusion criteria:** SSR

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Kovacs 2010 *(Continued)*

	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 25)
	Arm 2: long agonist plus rFSH (n = 25)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: various
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** oocyte number; number of embryos c yopreserved
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text m nuscr pt
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: no d clared
	Funding: unstated
	Author correspondence: yes p erkovacs1970@hotmail.com (16 September 2021)
	Calculations used t ob ain absolute event numbers: no
	Inclusion in meta-analy s: no (unclear risk of selection bias; primary review outcomes not reported)
	Additio al c mmen s: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unc ear risk	"random blocks".
Allocation concealment (selection bias)	Unc ear risk	Unstated.
Blinding of participan s and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.

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Kovacs 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Unclear registration status, however no evidence of selective reporting.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms. No other biases detected.

Ku 2003

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** South Korea **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 45
Participants	**Inclusion criteria:** uterine or perito eal factors, such as moderate to severe endometriosis, adenomyosis, or uterine myoma **Exclusion criteria:** unstated **Predicted response s s ted by the trialists:** unstated **Oocyte donors:** no **Cause of inferti y:** various **Subgr up (age):** no **Subgroup BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG & uFSH (n = 26) **Arm 2:** long agonist plus uFSH (n = 19) **F rtilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated

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Ku 2003 *(Continued)*

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: yes - shmoon@plaza.snu.ac.kr (16 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, howeve o ly objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, h wever only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Selective reporting not detected.
Other bias	Unclear isk	Trial conducted pre-2010. Trial conducted post-2010. Registration timeline unstated. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Kurzawa 2008

Study character stics

Methods

Design: randomised controlled trial

Country: Poland

Language: English

Setting: single centre

Recruitment period: from 2004 to 2006

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Kurzawa 2008 *(Continued)*

	Sample size (total randomised): 74
Participants	**Inclusion criteria:** age ≤35 years; PCOS (Rotterdam criteria); BMI <26 kg/m^2; FSH <12 mIU/ml on the third day of the cycle; negative screening for hepatitis B and C virus infection and HIV infection **Exclusion criteria:** ≥2 previous miscarriages; ≥3 unsuccessful IVF/ICSI cycles; anatomical abnormalities of the uterus on laparoscopy or hysteroscopy; ovarian cysts **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 37) **Arm 2:** long agonist plus rFSH (n = 37) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** clea age stage (days 2-4) **Luteal phase support:** oral dydrogesteron p s vaginal progesterone
Outcomes	**Outcomes reported:** live birth; se ere OH S; multiple pregnancy; miscarriage; oocyte number **Outcomes included in the met analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** ACT N12607000636459 **Registration date:** ns ated **Conflict of inte st declaration:** unstated **Fundi g:** uns ated **Author c r espondence:** yes - ciepiela@sci.pam.szczecin.pl (9 February 2021) **Calculations used to obtain absolute event numbers:** no **In usion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary utcomes [live birth and/or OHSS]) **Add ional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated random letters".
Allocation concealment (selection bias)	Unclear risk	"Allocations were concealed in opaque sealed envelopes", although unclear if sequentially numbered.

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Kurzawa 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding undertaken, although only objective outcomes suitable for meta-analysis.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding undertaken, although only objective outcomes suitable for meta-analysis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010 Sele tive re orting not detected.
Other bias	Low risk	Trial conducted pre-2010 S ngle entre tudy with plausible recruitment rates. No concerns regarding v lidity of re ults. Effect size difference lower than two-fold between trial arms. o other bia es detected.

Kyono 2004

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Japan **Language:** English **Setting:** single centre **Recruitment perio :** un tated **Sample size (to al randomised):** 73
Participants	**Inclusi n cri ria:** ag <40 years **Exclus n c iteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **C use of infertility:** unstated **Sub roup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus uFSH (n = 26) **Arm 2:** short antagonist plus uFSH & uhCG (n = 24) **Arm 3:** short antagonist plus uFSH (n = 23) **Fertilisation method:** unstated

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Kyono 2004 *(Continued)*

	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** OHSS; oocyte number
	Outcomes included in the meta-analysis: OHSS
Notes	**Type of publication:** conference abstract
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none undertaken (author c tact de ils not found)
	Calculations used to obtain absolute event nu bers: no
	Inclusion in meta-analysis: yes (sensitivity analysi includ ng all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support f r ju gement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Uns ated, and subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear isk	Unstated, and subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporti g (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Lahoud 2017

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Australia **Language:** English **Setting:** multicentre **Recruitment period:** 2007 to 2009 **Sample size (total randomised):** 100
Participants	**Inclusion criteria:** age 18-42 years; ≤3 previous stimulated IVF/ICSI tre tment cycles; not an oocyte donor; not already taken part in the study; no current endoc ne di order including pituitary disease, thyroid disease, or adrenal disease **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** u stated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 43) **Arm 2:** long agonist plus rFSH (n = 57) **Fertilisation method** I F or ICSI **Embryo age at the ime of t ansfer:** blastocyst (day 5+) **Luteal phase support:** vaginal progesterone
Outcomes	**Outc mes reported:** live birth; clinical pregnancy; multiple pregnancy; miscarriage; oocyte number **Outcomes ncluded in the meta-analysis:** live birth; clinical pregnancy; multiple pregnancy; miscarriage; oocyte n mber
Notes	**Type of publication:** published full-text manuscript **Tri l registration:** ACTRN12610000064000 **Reg stration date:** unstated **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

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Lahoud 2017 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Online computer-generated randomization".
Allocation concealment (selection bias)	Low risk	"Concealed allocation".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open trial, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open trial, however only objective o tcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to f llow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted a d publ shed pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. E ect size ifference lower than two-fold between trial arms. No other biases dete ted

Lainas 2007

Study characteristics

Methods	**Design:** n omised controlled trial **Coun ry:** Greece **Language:** nglish **Se ting:** single centre **Recru tment period:** January 2003 to January 2005 **Sample size (total randomised):** 78
Participants	**Inclusion criteria:** age 18-39 years; <3 previous IVF/ICSI attempts; no endometriotic cysts; basal FSH ≤10 IU/l; PCOS (presence of oligoovulation/anovulation and polycystic ovaries) **Exclusion criteria:** previous low ovarian response **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no

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Lainas 2007 *(Continued)*

	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 26)
	Arm 2: long agonist plus rFSH (n = 52)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** oocyte number
	Outcomes included in the meta-analysis: oocyte number
Notes	**Type of publication:** published full-text manuscrip
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - stratis.kol bian kis@irg.gr (23 February 2022)
	Calculations used to obtain abso ute event numbers: yes
	Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)
	Additional comments: -

Risk of bias

Bias	Authors' judgemen	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random allocation was performed by a study nurse on the basis of a computer-generated randomization list in a 1:2 ratio".
Allocation concealment (selection bias)	Low risk	"The responsible physicians (investigators) were not involved in the randomization process".
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Neither patients nor doctors were blinded to the treatment assigned", subjective outcomes (e.g., OHSS) reported.
Blinding of outcome assessment (detect on b as) All outcomes	High risk	"Neither patients nor doctors were blinded to the treatment assigned", subjective outcomes (e.g., OHSS) reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Attrition rate >10% in the GnRH agonist group.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.

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Lainas 2007 *(Continued)*

Other bias	Low risk	Single centre study with plausible recruitment rates. Trial conducted pre-2010.

Lainas 2008

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Greece **Language:** English **Setting:** single centre **Recruitment period:** June 2002 to July 2006 **Sample size (total randomised):** 270
Participants	**Inclusion criteria:** regular menstrual cycle (durati n 21–35 days); one or more failed IVF cycles, in which <6 oocytes were retrieved using a high gonadotrophin dose (≥300 IU/day) **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** p dicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antago ist plus rFSH (n = 180) **Arm 2:** agonist fl re plus rFSH (n = 90) **Fertil ation method:** IVF or ICSI **Embryo e at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Out mes reported:** clinical pregnancy; ongoing pregnancy; cancellation; oocyte number; number of embryos cryopreserved **Out omes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - stratis.kolibianakis@gmail.com (16 September 2021)

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Lainas 2008 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization list in a 1:2 atio".
Allocation concealment (selection bias)	Unclear risk	"Random allocation was performed by a study nurse , unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Neither patients nor doct rs we blind d to the treatment assigned", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Neither patients nor doctors were blinded to the treatment assigned", subjective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis perform Thirty-nine women were cancelled in the antagonist group, and 22 i the agonist group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Retrospec ively registered, however conducted pre-2010.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Lainas 2010

Study characteristics

Methods	**D sign:** randomised controlled trial **Country:** Greece **Language:** English **Setting:** single centre **Recruitment period:** November 2004 to February 2008 **Sample size (total randomised):** 220
Participants	**Inclusion criteria:** age 18-39 years; PCOS; no endometriotic cyst present, as assessed by transvaginal ultrasound examination; basal hormonal levels of FSH in the early follicular phase of ≤10 IU/ml **Exclusion criteria:** previous low ovarian response **Predicted response as stated by the trialists:** predicted high response

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Lainas 2010 *(Continued)*

	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 110)
	Arm 2: short antagonist plus rFSH (n = 110)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; ongoing preg ancy; oocyte number
	Outcomes included in the meta-analysis: OHSS
Notes	**Type of publication:** published full-text man script
	Trial registration: NCT00417144
	Registration date: 29 December 2006
	Conflict of interest declaration: nstated
	Funding: unstated
	Author correspondence: yes stratis kolibianakis@gmail.com (16 September 2021)
	Calculations used to obtain abs lute event numbers: no
	Inclusion in meta-analysis yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth nd/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated randomization list".
Allocation concealment (selection bias)	Uncl ar risk	Unstated.
Blinding of partic pan s and personnel (perfor mance bias) All outcomes	High risk	"Neither patients nor doctors were blinded to the treatment assigned", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Neither patients nor doctors were blinded to the treatment assigned", subjective outcomes reported.

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Lainas 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Retrospectively registered, however conducted pre-2010.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detec ed.

Lavorato 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Brazil **Language:** English **Setting:** single centre **Recruitment period:** May 2011 to Nov mber 2011 **Sample size (total randomised):** 32
Participants	**Inclusion criteria:** age ≤37 years; firs IVF ICSI cycle, BMI <30 kg/m^2; regular menses; presence of two normal ovaries **Exclusion criteria:** unstated **Predicted response as s ted by the trialists:** unstated **Oocyte donors:** no **Cause of infertil y:** various **Subg oup (a e):** no **Subgroup BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm** long agonist plus rFSH & rLH (n = 30) **Arm 2:** short antagonist plus rFSH & rLH (n = 30) **Fertilisation method:** unstated **Embryo age at the time of transfer:** N/A **Luteal phase support:** N/A
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis:** oocyte number
Notes	**Type of publication:** published full-text manuscript

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Lavorato 2012 *(Continued)*

Trial registration: unstated

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: yes - crh@crh.com.br; franco@crh.com.br (16 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection a d other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated table".
Allocation concealment (selection bias)	Low risk	As described by the authors on 20/09/2021 via email: "A registered nurse not involved in the recruit ng, assessment, or treatment of the patients was the responsable to kept the a computer generated table with the case numbers in a safe locked locat on and carried out the drawn lots were to determine the case number of e ch patient".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The sam techni an, blinded to subject identity, performed all examinations" On y objec ive outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The sa e technician, blinded to subject identity, performed all examinat ons". Only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Unclear ris	Trial published post-2010. Registration timeline unstated.
Other bias	Lo risk	The study was approved and controlled by the local Research Ethics Committee (Women's Health Reference Centre) project reference: 011/11 date 27/04/2011. First patients recruited 02/05/2011. First and last patients recruited 30/11/2011.

Lavy 1988

Study characteristics

Methods

Design: randomised controlled trial

Country: United States of America

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Lavy 1988 *(Continued)*

	Language: English
	Setting: single centre
	Recruitment period: January to April 1987
	Sample size (total randomised): 40
Participants	**Inclusion criteria:** age ≤37 years; regular menstrual cycles before IVF; tubal factor as the only known indication for IVF; normal SFA
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: tubal
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** hMG without pituitary suppression (n = 0)
	Arm 2: uFSH without pituitary suppression n = 20)
	Fertilisation method: IVF
	Embryo age at the time of transf r: leav ge stage (days 2-4)
	Luteal phase support: intramus ular progesterone
Outcomes	**Outcomes reported:** oocyte number
	Outcomes included n th meta-analysis: none
Notes	**Type of publicat on:** published full-text manuscript
	Trial regi tion unstated
	Regi ration date: -
	Conflict of terest declaration: unstated
	Fu ding: unstated
	Auth r correspondence: none undertaken (author contact details not found)
	Calc lations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned".

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Lavy 1988 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow p.
Selective reporting (reporting bias)	Low risk	Trial conducted and published p 2010 Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single ce tre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Lee 2011

Study characteristics	
Methods	**Design:** randomised controll d trial **Country:** China **Language:** English **Setting:** single centr **Recruitm t peri d:** September 2005 to September 2009 **Samp e size otal randomised):** 53
Participants	**Inclusion cr teria:** <4 oocytes retrieved in a previous failed IVF cycle or <5 antral follicles as assessed during the early follicular phase within 2 months preceding the IVF treatment cycle **Ex lusion criteria:** age >40 years; major medical illness; severe hepatic or renal impairment **Predicted response as stated by the trialists:** predicted low response **Oo yte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus letrozole & hMG (n = 26) **Arm 2:** short antagonist plus hMG (n = 27)

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Lee 2011 *(Continued)*

	Fertilisation method: IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** live birth; ongoing pregnancy; miscarriage; cancellation **Outcomes included in the meta-analysis:** live birth; ongoing pregnancy; miscarriage; cancellation
Notes	**Type of publication:** published full-text manuscript **Trial registration:** HKCTR-1158 **Registration date:** unstated **Conflict of interest declaration:** unstated **Funding:** "This study was supported by the Hong Kong OG Trus Fund." **Author correspondence:** yes - v200lee@hku.hk 6 Septemb r 2021) **Calculations used to obtain absolute event numb rs:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support or judgement
Random sequence generation (selection bias)	Low risk	"compu r-generated list".
Allocation concealment (selection bias)	Low risk	"sealed, opaque envelopes", centrally performed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	H gh ris	ITT analysis performed. Four women were cancelled in the letrozole plus hMG group, and two in the hMG group. Attrition >10% in the letrozole plus hMG group.
Selective repor g (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Lenton 2000

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United Kingdom **Language:** English **Setting:** multicentre **Recruitment period:** January 1997 to February 1998 **Sample size (total randomised):** 155
Participants	**Inclusion criteria:** pre-menopausal women aged 18-38 years whose infertility was attributable to tubal factor, grade I or II endometriosis, male factor, or unexplained infe tility; first cycle of ART; regular ovulatory cycles lasting 25-35 days; BMI 18-26 kg/m^2; both ovar s present; normal uterine cavity; no treatment with gonadotrophins in the month prior to the dy; willi gness to participate in the study and comply with procedures **Exclusion criteria:** previous low or over response to gonadot ophins; previous history of severe OHSS: PCOS; azoospermia or clinical signs of infection in SF **Predicted response as stated by the trialists:** predicted normal response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n 80) **Arm 2:** long agonist plus uFSH (n = 75) **Fertilisation me hod:** IVF or ICSI **Embry age a the time of transfer:** cleavage stage (days 2-4) **Luteal pha e support:** intramuscular or vaginal progesterone
Outcomes	**Outcomes reported:** live birth; OHSS; clinical pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number; number of cleavage-stage embryos; number of embryos cryopreserved **Outco es included in the meta-analysis:** live birth; OHSS; clinical pregnancy; multiple pregnancy; mis arriage; cancellation; oocyte number; number of cleavage-stage embryos; number of embryos cryopre erved
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** "Serono Pharmaceuticals (UK) Limited provided financial assistance and support." **Author correspondence:** yes - lizalenton@aol.com, ivf@lento.plus.com (30 September 2021)

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Lenton 2000 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation as confirmed by Van Wely 2011.
Allocation concealment (selection bias)	Low risk	SNOSE as confirmed by Van Wely 2011.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study, subjective outcomes (O SS) reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study, subjective outcomes (OHSS) reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis perform d. Fifteen women were cancelled in the rFSH group and eight in the uFSH gro . Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial c nduc ed nd published pre-2010. Selective reporting not detected.
Other bias	Low risk	T ial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Li 2016

Study characteristics

Methods

De ign: randomised controlled trial

Coun ry: China

Language: English

tting: single centre

Recruitment period: January 2014 to June 2015

Sample size (total randomised): 579

Participants

Inclusion criteria: age <38 years; first IVF cycle

Exclusion criteria: unstated

Predicted response as stated by the trialists: unstated

Oocyte donors: no

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Li 2016 *(Continued)*

	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & hMG (n = 275)
	Arm 2: long agonist plus rFSH (n = 304)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** ongoing pregnancy; oocyte numb r
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** conference abstract
	Trial registration: ChiCTR-TRC-14004965
	Registration date: 22 June 2014
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none unde taken (author contact details not found)
	Calculations used to obtain bsolut event numbers: no
	Inclusion in meta-analysis: no nclear risk of selection bias [allocation concealment unstated]; primary review outcom s no reported)
	Additional commen s -

Risk of bias

Bias	Auth rs' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation list".
Allocation concealment (selection bias)	Uncle r risk	Unstated.
Blinding of partic pants and personnel (erformance bias) All outcomes	w risk	Open label, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open label, however only objective outcomes reported.
Incomplete outcome data (attrition bias)	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Attrition rate >10% in both arms.

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Li 2016 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken within six months of recruitment commencement. No evidence of selective reporting.
Other bias	Low risk	Trial conducted post-2010 and registered within six months of first patient recruitment. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Lin 2006

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** single centre **Recruitment period:** July 2003 to December 2 04 **Sample size (total randomised):** 120
Participants	**Inclusion criteria:** age 20–38 years; r gular cycles; normal basal hormonal profile (day-3 FSH <10 mIU/ml, LH <10 mIU/ml and oestradiol 60 pg/ml), BMI 18.5-24.9 kg/m^2; male factor infertility **Exclusion criteria:** endometrio is; an ulation; PCOS; hydrosalpinx **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility** male fa tor **Subgroup (age):** no **Subgroup (B I):** yes <30 kg/m^2) **Subgro p (thnicity):** no
Interventions	**Arm 1:** short antagonist plus clomifene citrate & hMG (n = 60) **Ar 2:** long agonist plus rFSH & hMG (n = 60) **Fer ilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; miscarriage; cancellation; oocyte number **Outcomes included in the meta-analysis:** live birth; clinical pregnancy; miscarriage; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated

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Lin 2006 *(Continued)*

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"blocked randomisation"
Allocation concealment (selection bias)	Low risk	"sealed envelopes", and linicians not aware of the allocation until the patients were about to start stimulation.".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unclear, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unclear, owever nly objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	TT ana ysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	ial conducted and published pre-2010.Selective reporting not detected.
Other bias	Low sk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Lisi 2012

Study characteris cs

Methods

Design: randomised controlled trial

Country: Italy

Language: English

Setting: single centre

Recruitment period: June 2009 to December 2010

Sample size (total randomised): 150

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Lisi 2012 *(Continued)*

Participants	**Inclusion criteria:** age <40 years; BMI 18-20 kg/m^2; baseline FSH <10 IU/l; first or second attempt at IVF/ICSI **Exclusion criteria:** ovulation induction or any other hormone treatment in the three months preceding the study; endometriosis; PCOS **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 75) **Arm 2:** long agonist plus rFSH & rLH (n = 75) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** unstated **Luteal phase support:** vaginal progestero e
Outcomes	**Outcomes reported:** clinical pregnancy; oocy number **Outcomes included in the meta- nalysis** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declara ion:** none declared **Funding:** unstat d **Autho corre pondence:** yes - franco.lisi01@gmail.com (23 February 2022) **Calculat s used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias; primary review outcomes not reported) **Ad itional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence ge era-tion (selection bias)	Unclear risk	"block randomization".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (perfor-mance bias)	Low risk	"Open-label", however only objective outcomes reported.

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Lisi 2012 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Open-label", however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Study conducted pre-2010. Single centre tri l with plausible recruitment rates.

Liu 2015

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** single centre **Recruitment period:** January 2009 o December 2011 **Sample size (total randomis d):** 50
Participants	**Inclusion criteria:** age >37 years; BMI 19-30 kg/m^2; basal FSH <10 IU/l and oestradiol <80 pg/ml, ≥10 antral follicles; regular menstrual cycles of 25-35 days; <3 previous failed cycles; normal uterine cavity as assessed through hystero alpingogram or hysteroscopy; normal TSH level **Exclusion criter a:** POI; previous poor response; history of severe OHSS; PCOS; untreated hydrosalpinx; co aindic tion to pregnancy, thyroid or adrenal dysfunction; neoplasia; severe impairment of renal o hepat c function; use of medications that might interfere with study evaluations (e.g., hormonal m icatio , prostaglandin inhibitors, and psychotropic agents) **Predicted r sponse as stated by the trialists:** unstated **O cyte donors:** no **Cause of infertility:** various **Subgroup (age):** yes (≥35 years) **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus uFSH & rLH (n = 254) **Arm 2:** long agonist plus rFSH & rLH (n = 254) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4)

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Liu 2015 *(Continued)*

	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; miscarriage; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** "This work was supported by the National Basic Res rch Program (81170622) and Yantai City Science and Technology Fund Planning Project of China (2011222). Liu Xuemei, Hao Cuifang and Wang Jinfang have no conflicts of interest to declare." **Author correspondence:** yes - yyyhcf@yeah.net 16 Septem er 2021) **Calculations used to obtain absolute event numbers:** yes **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support or udgement
Random sequence generation (selection bias)	Low risk	"compute generated randomization number sequence".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjectives outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjectives outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed. Absolute numbers obtained by calculation from percentages. Eleven women cancelled in each group (total = 22). Attrition >10%.
Selective reporting (r porting bias)	Unclear risk	Registration status unstated, trial conducted post-2010.
Other bias	Unclear risk	Trial conducted post-2010. Registration timeline unstated. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Liu 2018

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** single centre **Recruitment period:** June 2015 to June 2016 **Sample size (total randomised):** 320
Participants	**Inclusion criteria:** age 22-40 years; regular menstrual cycles (24-35 days), AFC 5 and serum FSh <10 IU/l at baseline **Exclusion criteria:** endometriosis grade III or higher; diagnosis of PCOS; administration of hormonal treatments within the 3-month period prior to the study; co traindications to COS **Predicted response as stated by the trialists:** u stated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** progestogen plus clomifen citrate & hMG (n = 160) **Arm 2:** progestogen plus hMG (= 160) **Fertilisation method** I F or ICSI **Embryo age at the ime of t ansfer:** various **Luteal phase support:** freeze-all policy
Outcomes	**Outc mes reported:** live birth; ongoing pregnancy; miscarriage; ectopic pregnancy; cancellation; oocyte umber; number of cleavage-stage embryos; number of blastocysts; number of embryos cryop-reserved **O tcomes included in the meta-analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Tria registration:** ChiCTR-IPR-15006521 **Registration date:** 1 June 2015 **Conflict of interest declaration:** none declared **Funding:** "Shanghai Three - year Plan on Promoting TCM Development, Grant/Award Number: ZY3-LCPT-2-2006; National Nature Science Foundation of China, Grant/Award Number: 81571397, 81503603 and 81671520; Natural Science Foundation of Shanghai, Grant/Award Number: 15401932700 and 15ZR1424900" **Author correspondence:** yes - kuangyanp@126.com (15 September 2021) **Calculations used to obtain absolute event numbers:** no

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Liu 2018 *(Continued)*

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomization list".
Allocation concealment (selection bias)	Unclear risk	Allocation was performed via "number d and seal envelopes", although unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial, subjective outcomes re orted.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed T n women cancelled in the clomifene citrate group, and forteen in the hMG-only group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conduc ed post-2010. Registration undertaken prospectively. All outcomes repor d as stated in the registration. No evidence of selective reporting.
Other bias	Low risk	Trial onducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold be- we n trial arms.

Liu 2020

Study characteristics

Methods	**Design:** randomised controlled trial **Coun ry:** China **Language:** English **Setting:** single centre **Recruitment period:** September 2013 to September 2015 **Sample size (total randomised):** 201
Participants	**Inclusion criteria:** low ovarian response (Bologna criteria) **Exclusion criteria:** repeated failure in IVF (numbers of cycle ≥ 2); severe endometriosis or adenomyosis; PCOS; allergy or contraindication to gonadotropin; participation in other clinical studies at the same time

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Liu 2020 *(Continued)*

	Predicted response as stated by the trialists: predicted low response
	Oocyte donors: no
	Cause of infertility: low ovarian reserve
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus letrozole plus rFSH (n = 101)
	Arm 2: long agonist plus rFSH (n = 100)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; ngoing pregnancy; miscarriage; oocyte number
	Outcomes included in the meta-analysis: live birth
Notes	**Type of publication:** published full-text m nuscr pt
	Trial registration: ChiCTR-TRC-1300345
	Registration date: 6 August 2013
	Conflict of interest declaration: no d clared
	Funding: none sought
	Author correspondence: yes d uangr@sina.com, liuxp6@foxmail.com (5 February 2021)
	Calculations used t ob ain absolute event numbers: no
	Inclusion in meta-analy s: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live bi th and/or OHSS])
	Addit onal comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	L w risk	"random number table".
Allocation conce lment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded, subjective outcomes performed (e.g., cancellation).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded, subjective outcomes performed (e.g., cancellation).

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Liu 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	ITT not performed - cumulative pregnancy outcomes reported instead. Attrition rates <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. Selective reporting not detected.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Long 1995

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 70
Participants	**Inclusion criteria:** age 25-45 years; rst IV cycle **Exclusion criteria:** unstated **Predicted response as stated b the trialists:** unstated **Oocyte donors:** no **Cause of inferti ty:** un t ted **Subgro p (a e):** no **Subg oup (BMI):** no **Subgroup (e hnicity):** no
Interventions	**Arm 1:** agonist flare plus hMG (n = 36) **A m 2:** clomifene citrate plus hMG without pituitary suppression (n = 34) **Fert isation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** none
Outcomes	**Outcomes reported:** cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated

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Long 1995 *(Continued)*

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: none undertaken (author contact details not found)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, howeve o ly objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, h wever only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Absolute event numbers reported for ITT analysis. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear isk	Trial conducted pre-2010. Single centre study with unclear recruitment rate due to unstated timeline.

Loumaye 1989

Study characteris cs

Methods

Design: randomised controlled trial

Country: Belgium

Language: English

Setting: single centre

Recruitment period: unstated

Sample size (total randomised): 18

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Loumaye 1989 *(Continued)*

Participants	**Inclusion criteria:** age <40 years; tubal infertility; two ovaries **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** tubal **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus hMG (n = 9) **Arm 2:** long agonist plus hMG (n = 9) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** hCG
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis** o e
Notes	**Type of publication:** published fu -text m nuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not found) **Calcul tions sed to obtain absolute event numbers:** no **Inclusio i meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequen e ge era-tion (selection bias)	Unclear risk	"randomly divided", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (perfor-mance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.

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Loumaye 1989 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis performed. Attrition unstated.
Selective reporting (reporting bias)	Unclear risk	Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single cent e study, uncl ar recruitment timeline.

Loutradis 1998

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Greece **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 72
Participants	**Inclusion criteria:** unstated **Exclusion criteria:** unstated **Predicted response as tat d by the trialists:** unstated **Oocyte donors:** no **Cause f infe tility:** stated **Subgr up (ge):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Ar 1:** long agonist plus rFSH (n = 40) **Arm 2:** long agonist plus hMG (n = 32) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** cancellation **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract

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Loutradis 1998 *(Continued)*

Trial registration: unstated

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection and other biases primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjec ve outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, su jective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT nalysis performed for the included outcomes. Attrition >10% in group B.
Selective reporting (reporting bias)	Low ri k	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Unclear recruitment rates as study duration unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Loutradis 2004a

Study characteristics

Methods

Design: randomised controlled trial

Country: Greece

Language: English

Setting: single centre

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Loutradis 2004a *(Continued)*

	Recruitment period: unstated
	Sample size (total randomised): 116
Participants	**Inclusion criteria:** age 20-38 years; no low response in a previous treatment cycle; no uterine or ovarian anomalies; history of regular menstrual cycles (25 to 35 days)
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unselected population
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 58)
	Arm 2: short antagonist plus rFSH (n = 58)
	Fertilisation method: unstated
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: hCG
Outcomes	**Outcomes reported:** clinical preg ancy; o cyte number; number of embryos cryopreserved
	Outcomes included in the meta- alysis: none
Notes	**Type of publication:** publ hed f ll-text manuscript
	Trial registration: unstated
	Registration dat : -
	Conflict teres declaration: unstated
	Fund ng: uns ated
	Author cor spondence: yes - kstef@compulink.gr (15 September 2021)
	Ca culations used to obtain absolute event numbers: no
	Inclu ion in meta-analysis: no (unclear risk of selection bias [allocation concealment unstated]; prima y review outcomes not reported)
	Add tional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was accomplished using a computer-generated randomization table."
Allocation concealment (selection bias)	Unclear risk	"The sequences of randomization were concealed until intervention was assigned", unstated how.

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Loutradis 2004a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010 Sele tive re orting not detected.
Other bias	Low risk	Trial conducted pre-2010 S ngle entre tudy with plausible recruitment rates. No concerns regarding v lidity of re ults. Effect size difference lower than two-fold between trial arms. o other bia es detected.

Lukaszuk 2015

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Poland **Language:** English **Setting:** multicentre **Recruitment perio :** Jul 2013 to January 2014 **Sample size (to al randomised):** 298
Participants	**Inclusi n crit ria:** ag <40 years; AMH >0.6 ng/ml; BMI 18-29 kg/m^2; ICSI treatment **Exclus n c iteria:** endometriosis; preimplantation diagnosis **Predicted response as stated by the trialists:** unstated **O cyte donors:** no **C use o infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 154) **Arm 2:** agonist flare plus hMG (n = 144) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** blastocyst (day 5+)

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Lukaszuk 2015 *(Continued)*

	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; multiple pregnancy; miscarriage; ectopic pregnancy; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** IRCT2015020418202N4 **Registration date:** 27 February 2015 **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - krzysztof.lukaszuk@invicta.p (16 September 2021) **Calculations used to obtain absolute event numbe** no **Inclusion in meta-analysis:** yes (sensitivity analysis - includi g all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgem nt
Random sequence generation (selection bias)	Low risk	"block random zation software".
Allocation concealment (selection bias)	Low risk	"complete llocation concealment".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The doctors performing the oocyte retrieval procedure and the embryologist involved were blind to the treatment groups", although only objective out ome events reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The doctors performing the oocyte retrieval procedure and the embryologists involved were blind to the treatment groups".
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Twenty women did not undergo embryo transfer in the long agonist group, and 24 in the short agonist group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low isk	Trial conducted post-2010. Registration details unstated. Selective reporting not detected.
Other bias	High risk	Trial conducted post-2010. Retrospectively registered as confirmed by the trial authors. Multicentre study. Effect size difference lower than two-fold between trial arms.

Madani 2012

Study characteristics

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Madani 2012 *(Continued)*

Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** October 2009 to March 2011 **Sample size (total randomised):** 73
Participants	**Inclusion criteria:** predicted low response according to at least two of the following criteria: advanced maternal age (37-43 years), AFC <5, prior history of low response to COS; indication for ICSI treatment (second or third cycle); BMI ≤30 kg/m^2; two functional ovaries and no previous ovarian surgery; normal uterine cavity; normal tubes based on recent hysterosalpingography or hysteroscopic evaluation; basal (day 2 or 3) serum FSH levels ≤13 IU/l; normal SFA; no history or signs of endometriosis; no untreated endocrine disease **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 26) **Arm 2:** long agonist plus rFSH & uhCG (n = 47) - two arms merged (see additional comments) **Fertilisation method:** ICSI **Embryo age at the time transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; oocyte number **Outcomes included in the meta-analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT01509833 **Registration date:** 13 January 2012 **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - tmadani@royaninstitute.org (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

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Madani 2012 *(Continued)*

	Additional comments: Group A received recombinant FSH alone (n = 26), group B received recombinant FSH supplemented by 100 IU hCG (n = 24) and group C received recombinant FSH supplemented by 200 IU hCG (n = 23). For the purposes of meta-analysis, groups B and C were amalgamated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"permuted block randomisation method".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective tcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only obje tive outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. N loss to follow-up.
Selective reporting (reporting bias)	Low risk	Re ospec ively registered. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre- and post-2010. Retrospectively registered. Single centre study h plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms.

Maity 2010

Study characteristics

Methods	**Design:** randomised controlled trial **Co ntry:** India **Language:** English **Setting:** single centre **Recruitment period:** October 2007 to September 2008 **Sample size (total randomised):** 33
Participants	**Inclusion criteria:** age <37 years; normo-ovulatory; second ART cycle following treatment failure or miscarriage **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated

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Maity 2010 *(Continued)*

	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 17)
	Arm 2: long agonist plus rFSH & hMG (n = 16)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** serum LH, progesterone an oestradio evels; implantation rate; clinical pregnancy; ongoing pregnancy; oocyte number; embr o quality
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** conference abstract
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: ns ated
	Funding: unstated
	Author correspondence: none ndertaken
	Calculations used to obt in absolute event numbers: no
	Inclusion in meta-a a ysis: no (insufficient data in the abstract; author contact details not found)
	Additional comments: -

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomised", methodology unstated.
Allocation concealment (selection bias)	Uncl ar risk	Unstated.
Blinding of partic pan s and personnel (perfor mance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.

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Maity 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed. Attrition unclear.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rate. No other sources of bias identified.

Mak 2017

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** single centre **Recruitment period:** March 2012 to September 2015 **Sample size (total randomised):** 50
Participants	**Inclusion criteria:** predicted low esponse (Bologna criteria) **Exclusion criteria:** BMI ≥30 kg/m absence of one ovary; PCOS; presence of uterine abnormalities or endocrine, metabolic and aut immune disease **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of inferti ty:** va us **Subgro p (age):** no **Subgr up (BMI):** yes (<30 kg/m^2) **Subgroup (e hnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH & rLH (n = 25) **Arm 2:** short antagonist plus rFSH & uhCG (n = 25) **Fert lisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; miscarriage; cancellation; oocyte number **Outcomes included in the meta-analysis:** live birth; clinical pregnancy; miscarriage; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript

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Mak 2017 *(Continued)*

Trial registration: ChiCTRTRC-12002072

Registration date: 4 April 2012

Conflict of interest declaration: none declared

Funding: "Serono HK Ltd provided the rLH (Pergoveris or Luveris) for the study but the company did not have any involvement in the planning, execution, monitoring and analysis of data relating to the study."

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of se ction and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random mbers".
Allocation concealment (selection bias)	Low risk	"Opaque envelop s Research nurse coordinated the randomization process".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All patients and personnel blinded to the allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blindin undertaken.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not performed but possible to extract absolute even numbers from the manuscript. A total of four women discontinued the intervention in the uhCG group, and seven in the rLH group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low ris	Trial conducted post-2010 and registered within six months of first recruited participant. Selective reporting not detected.
Other bias	Low risk	Trial conducted post-2010 and registered within six months of first recruited participant. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms. No other biases detected.

Maldonado 2013

Study characteristics

Methods

Design: randomised controlled trial

Country: Brazil

Language: English

Setting: single centre

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Maldonado 2013 *(Continued)*

	Recruitment period: unstated
	Sample size (total randomised): 96
Participants	**Inclusion criteria:** age <37 years; regular menstrual cycles (25–35 days); normal basal FSH and LH levels; BMI <30 kg/m^2; presence of both ovaries and intact uterus; absence of polycystic ovaries, endometriosis or gynaecological/medical disorders; negative result in a screening for sexually transmitted diseases
	Exclusion criteria: no hormonal therapy within the sixty days preceding the study
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** agonist flare plus rFSH & rhCG (n = 48)
	Arm 2: short antagonist plus rFSH & rhCG (n = 48)
	Fertilisation method: ICSI
	Embryo age at the time of transfe : b stocyst (day 5+)
	Luteal phase support: vag al progestero e
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; miscarriage; oocyte number
	Outcomes included in the meta analysis: OHSS
Notes	**Type of publication** published full-text manuscript
	Trial registration: uns t d
	Registr tion date:
	Confl ct of i terest declaration: none declared
	Funding: uns ated
	Au hor correspondence: yes - science@sapientiae.org.br (16 September 2021)
	Calcul tions used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization table".

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Maldonado 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	"allocated by a single nurse" not involved in the trial design.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow p.
Selective reporting (reporting bias)	Low risk	Trial published post-2010 Regis ation meline unstated. Selective reporting not detected.
Other bias	Unclear risk	Trial published pre-2010. ngle cen re study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Malmusi 2005

Study characteristics	
Methods	**Design:** randomised controll d trial **Country:** Italy **Language:** English **Setting:** single centr **Recruitm t peri d:** unstated **Samp e size otal randomised):** 55
Participants	**Inclusion cr teria:** predicted low response **Exclusion criteria:** azoospermia **Predi ted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus rFSH (n = 30) **Arm 2:** short antagonist plus rFSH (n = 25) **Fertilisation method:** ICSI

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Malmusi 2005 *(Continued)*

	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** cancellation; oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - antlamarca@libero it (6 September 2021)
	Calculations used to obtain absolute event nu bers: no
	Inclusion in meta-analysis: no (unclear risk of sele tion an other biases; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support f r ju gement
Random sequence generation (selection bias)	Low risk	"randomiza ion l st".
Allocation concealment (selection bias)	Unclear risk	stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Uns ated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporti g (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Marci 2005

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** January 2001 to December 2002 **Sample size (total randomised):** 60
Participants	**Inclusion criteria:** age 32-44 years; serum oestradiol <600 pg/ml; low varian esponse **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted w response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 30) **Arm 2:** short antagonist plus rFSH (n = 30) **Fertilisation method:** IVF or ICSI **Embryo age at the tim of transfer:** cleavage stage (days 2-4) **Luteal phase support:** micronised vaginal progesterone
Outcomes	**Outcomes repor ed:** clinical pregnancy; ongoing pregnancy; cancellation; oocyte number **Outcomes in uded in the meta-analysis:** none
Notes	**Type of pu lication:** published full-text manuscript **Tr al registration:** unstated **Regi tration date:** - **Con ict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - robertomarci@tin.it (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias; primary review outcomes not reported) **Additional comments:** -
Risk of bias	

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Marci 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized 1:1 into the two treatment groups", no additional details provided.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. ttrition >10% in one of the trial arms (group A).
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre 2010. Single centre study with plausible recruitment rates. No concerns regard validity of results. Effect size difference lower than two-fold between tr al arms. No other biases detected.

Marrs 2004a

Study characteristics	
Methods	**Design:** randomised c ntrol ed trial **Country:** United States of America **Lang age:** English **Setting:** m lticentre **Re ruitment period:** unstated **Sample size (total randomised):** 431
Participants	**Inclusion criteria:** age 18–40 years; serum/plasma FSH ≤11.2 mIU/ml; presence of both ovaries; male factor infertility; and a requirement for ICSI for assisted reproduction **Exclusion criteria:** clinically significant systemic disease; smoking (>10 cigarettes/day); any contraindication to pregnancy; serum/plasma LH:FSH ratio >2; >2 previous ICSI cycles in which gonadotrophin stimulation was used **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** male factor **Subgroup (age):** no

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Marrs 2004a *(Continued)*

	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 212)
	Arm 2: long agonist plus rFSH (n = 219)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: progesterone (route unstated)
Outcomes	**Outcomes reported:** clinical pregnancy; oocyte number; number of embryos ryopreserved
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscrip
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - eduardo.k lly@serono.com (16 September 2021)
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: no (unc ar isk of selection bias [allocation concealment unstated]; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	S pport for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated sequence was used".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open label" trial, subjective outcomes reported.
Blinding of outco e assessment (detection ias) All outcomes	High risk	"open label" trial, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Eight women were cancelled in the rFSH/rLH group, and seventeen in the rFSH-only group. Attrition rate <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Marrs 2004a *(Continued)*

Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Martínez 2008

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** January 2005 to Novembe 2006 **Sample size (total randomised):** 323
Participants	**Inclusion criteria:** oocyte donor; age <35 years; baseline FSH <10 IU; BMI <30 kg/m^2; no history of hereditary disease; normal examination results **Exclusion criteria:** PCOS **Predicted response as stated by the trialists:** unstated **Oocyte donors:** yes **Cause of infertility:** N/A **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** lo g gonis plus hMG (n = 160) **Arm** short ntagonist plus rFSH (n = 163) **Fertilisati method:** N/A **Embryo age at the time of transfer:** N/A **Lute l phase support:** N/A
Outcomes	**Outcomes reported:** cancellation; oocyte number **Outcomes included in the meta-analysis:** cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** "This study has been conducted with the support of the Chair in Obstetric and Gynaecological Research of the Institut Universitari Dexeus."

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Martínez 2008 *(Continued)*

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The Biostatistics Department of our centre g nerated a randomization table using the SAS statistical package".
Allocation concealment (selection bias)	Low risk	"The researcher was blind to randomizati n (…). Once a donor had been recruited into the study the treatment group was assigned by means of a telephone call to the Biostatisti partm nt".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective ou omes repo ed (e.g., cancellation).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subject e outcomes reported (e.g., cancellation).
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analy s p rfo med. Attrition >10% in the long agonist group.
Selective reporting (reporting bias)	Low risk	Selecti e reporting not detected.
Other bias	Low risk	Sing e centre study with plausible recruitment rates. Study conducted pr 2010.

Martinez 2010

Study characteristics

Methods	**Design:** randomised controlled trial **Cou try:** Spain **L nguage:** English **Setting:** single centre **Recruitment period:** May to December 2007 **Sample size (total randomised):** 84
Participants	**Inclusion criteria:** age 18-35 years; oocyte donor; FSH <10 IU; BMI <30 kg/m^2; no history of hereditary disease; normal results on all tests performed **Exclusion criteria:** unstated

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Martinez 2010 *(Continued)*

	Predicted response as stated by the trialists: unstated
	Oocyte donors: yes
	Cause of infertility: N/A
	Subgroup (age): no
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH & hMG (n = 44)
	Arm 2: long agonist plus rFSH & hMG (n = 40)
	Fertilisation method: N/A
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** cancellation; oocyte number
	Outcomes included in the meta-analysis: cancellation; oocyte number
Notes	**Type of publication:** published full-text m n script
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaratio : uns t d
	Funding: "This work was performed under the auspices of the Catedra de Investigacion en Obstetricia y Ginecologıa del Insitut Univers tari Dexeus."
	Author correspondence none undertaken
	Calculations used t btain absolute event numbers: no
	Inclusion i met analysis: yes (primary analysis - low risk of selection and other biases)
	Addit onal comments: -

Risk of bias

Bias	Au hors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned (…) sing a randomization table using SAS software".
Allocation concealment (selection bias)	Low risk	"Researcher was blind to randomization".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., cancellation).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., cancellation).

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Martinez 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Study conducted pre-2010. Single centre trial with plausible recruitment rates.

Matorras 2009

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** January 2005 to November 2006 **Sample size (total randomised):** 131
Participants	**Inclusion criteria:** BMI 18-30 kg/m ; ba eline FSH <10 IU/l; normal baseline LH and oestradiol; presence of both ovaries and uterine c vit capable of sustaining a pregnancy; clomifene citrate or gonadotrophin wash out ≥30 days prio to starting GnRH agonist; confirmed absence of pregnancy; and signed informed consent **Exclusion criteria:** HIV, HBV or CV infection; clinically significant conditions presenting contraindication to gonadotrophin treatmen ; >2 previous cycles of ART **Predicted response as tat d by the trialists:** unstated **Oocyte donors:** no **Cause infe tility:** arious **Subgr up (ge):** yes (≥35 years) **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Ar 1:** long agonist plus rFSH (n = 68) **Arm 2:** long agonist plus rFSH & rLH (n = 63) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number **Outcomes included in the meta-analysis:** live birth; clinical pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number

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Matorras 2009 *(Continued)*

Notes	**Type of publication:** published full-text manuscript **Trial registration:** EudraCT2004-001503-36 **Registration date:** 14 October 2014 **Conflict of interest declaration:** unstated **Funding:** "This study was partially supported by a grant from Merck Farma y Quimica, SL, an affiliate of Merck, Darmstadt, Germany." **Author correspondence:** yes - roberto.matorras@osakidetza.net (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selectio and o her biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated number list".
Allocation concealment (selection bias)	Low risk	"sealed envelopes", SNOSE confirmed by Roberto Matorras on 17/09/2021.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open label" trial, ubjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open label" trial, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Three cycles in the rFSH group and no cancellations in the rFSH/rLH group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Mayenga 2006

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** France **Language:** English

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Mayenga 2006 *(Continued)*

	Setting: single centre
	Recruitment period: 2005
	Sample size (total randomised): 114
Participants	**Inclusion criteria:** age 25-38 years; normo-ovulatory cycles; first ART cycle
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 58)
	Arm 2: long agonist plus rFSH (n = 56)
	Fertilisation method: unstated
	Embryo age at the time of transfer: u stated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** oocyte n mbe ; number of transferred embryos; pregnancy rate; ongoing pregnancy; number of embryos c yopreserved
	Outcomes included in the met -analysis: none
Notes	**Type of publication** con erence abstract
	Trial registratio : un tated
	Registrat date
	Conf ct of in erest declaration: unstated
	Funding: u stated
	Au hor correspondence: none undertaken
	Calculations used to obtain absolute event numbers: no
	Incl sion in meta-analysis: no (insufficient data in the abstract; author contact details not found)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.

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Mayenga 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed. Attrit on unstated.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Single centre trial with plau ible ecruit ent rates. Conducted pre-2010. No other sources of bias ide tified.

Meden-Vrtovec 2003

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Slovenia **Language:** English **Setting:** single centre **Recruitment period:** u stated **Sample size (total andom ed):** 131
Participants	**Inclusion criteri** age 18-38 years; regular, ovulatory menstrual cycles; LH level <10 IU/l on day 3 of the me strua cycle; BMI <25 kg/m^2; tubal factor as the only cause of infertility; normal uterine cavity; no clinical y relevant findings regarding haematology, clinical chemistry or urinary analysis evaluations; normal SFA **Exclusion criteria:** unstated **P dicted response as stated by the trialists:** unstated **Oo yte donors:** no **Cau e of infertility:** tubal **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** rFSH without pituitary suppression (n = 70) **Arm 2:** uFSH without pituitary suppression (n = 61) **Fertilisation method:** IVF

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Meden-Vrtovec 2003 *(Continued)*

	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: hCG
Outcomes	**Outcomes reported:** OHSS; ectopic pregnancy; oocyte number
	Outcomes included in the meta-analysis: OHSS
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - helena.meden@kclj si (6 September 2021)
	Calculations used to obtain absolute event nu bers: no
	Inclusion in meta-analysis: yes (sensitivity analysi includ ng all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support f r ju gement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Uns ated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unc ar risk	Unclear if ITT analysis performed but possible to obtain absolute event numbers. Loss to follow-up unclear.
Selective reporti g (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Mehrabian 2021

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** 2018 **Sample size (total randomised):** 86
Participants	**Inclusion criteria:** low ovarian response (Bologna criteria) **Exclusion criteria:** metabolic endocrine diseases including hyperpro actinaemia, hypo or hyperthyroidism; endometriosis; history of previous ovarian su ery; BM >30 kg/m^2; azoospermia **Predicted response as stated by the trialists:** p edicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus letrozo & r SH (n = 43) **Arm 2:** short antagonist plus rFSH (n 43) **Fertilisation method:** unstat d **Embryo age at the ime of transfer:** cleavage stage (days 2-4) **Luteal phase su port:** ginal progesterone
Outcomes	**Outcomes re orted:** ocyte number **Outco es i cluded in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Tr l registration:** unstated **Registration date:** - **Con lict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - naghshineh@med.mui.ac.ir (23 November 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

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Mehrabian 2021 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Random allocation software".
Allocation concealment (selection bias)	Unclear risk	"Random allocation software".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes repo ted.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective o comes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to f llow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted p st 201 Registration timeline unstated. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted post-2010. Registration timeline unstated.

Melo 2010

Study characteristics

Methods	**Design:** randomi ed ontro ed trial **Country:** pain **Lang age:** English **Setting:** si gle centre **Re ruitment period:** January 2005 to December 2007 **Sample size (total randomised):** 1028
Participants	**Inclusion criteria:** female age 18-34 years; regular menstrual cycles; no family history of hereditary or chromosomal diseases, normal karyotype, and BMI 18-29 kg/m^2; negative screening for sexually transmitted diseases **Exclusion criteria:** PCOS **Predicted response as stated by the trialists:** unstated **Oocyte donors:** yes **Cause of infertility:** N/A **Subgroup (age):** yes (<35 years) **Subgroup (BMI):** yes (<30 kg/m^2)

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Melo 2010 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 346) **Arm 2:** long agonist plus hMG (n = 333) **Arm 3:** long agonist plus rFSH & hMG (n = 349) **Fertilisation method:** N/A **Embryo age at the time of transfer:** N/A **Luteal phase support:** N/A
Outcomes	**Outcomes reported:** OHSS; cancellation; oocyte number **Outcomes included in the meta-analysis:** OHSS; cancellati n; oocyte number
Notes	**Type of publication:** published full-text manuscrip **Trial registration:** NCT00829075 **Registration date:** 26 January 2009 **Conflict of interest declaration:** "M.M. has n thing to disclose. J.B. has nothing to disclose. N.G. has nothing to disclose. M.M. has nothing to disclos A.P. has nothing to disclose. J.R. has nothing to disclose." **Funding:** unstated **Author correspondence:** none undertake **Calculations used to obtain a solut vent numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	**Authors' judgem nt**	**Support for judgement**
Random sequence generation (selection bias)	Low r sk	"Computer-generated random numbers."
Allocation concealment (selection bias)	Low risk	"The study nurse coordinated the randomization process and distribution of medication throughout the controlled ovarian stimulation cycles. All embryologists, laboratory personnel, and sponsor staff, including the statistician responsible for the statistical analysis, were blinded to the treatment allocation."
Blinding of partic pants and personnel (p rfor mance bias) All outcomes	Low risk	Blinding undertaken.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding undertaken.
Incomplete outcome data (attrition bias)	High risk	ITT analysis performed. Sixty-two women cancelled in group 1, 53 in group 2 and 59 in group 3. Attrition >10% in all trial arms.

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Melo 2010 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Miller 2015

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 122
Participants	**Inclusion criteria:** age 18-42 years **Exclusion criteria:** unstated **Predicted response as stat d by he trialists:** unstated **Oocyte donors:** no **Cause of infertility:** uns ted **Subgroup (age):** no **Subgroup (BMI)** no **Subgr up (et nicity):** no
Interventions	**Arm 1:** long agonist plus hMG & uFSH (n = 60) **Arm 2:** long agonist plus hMG (n = 62) **Ferti isation method:** unstated **Emb yo age at the time of transfer:** unstated **L teal phase support:** unstated
Outcomes	**Outcomes reported:** live birth; OHSS; multiple pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** live birth; OHSS
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated

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Miller 2015 *(Continued)*

Funding: "Sponsored by Ferring Pharmaceuticals."

Author correspondence: none undertaken (author contact details not found)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open-label study", subjecti out omes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open-label study" subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT ana ysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	T ial published post-2010. Registration details not provided. Selective report- ng ot detected.
Other bias	Low risk	Trial post-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Miron 1998

Study characteristics

Methods	**Des gn:** randomised controlled trial **Country:** Canada **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 111
Participants	**Inclusion criteria:** age 18-38 years; regular ovulatory menstrual cycles (21-35 days); tubal factor, mild endometriosis or unexplained infertility; early follicular FSH levels normal; both ovaries intact; ≤3 previ-

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Miron 1998 *(Continued)*

	ous ART cycles; no assisted conception treatment for at least one full menstrual cycle; normal uterine cavity **Exclusion criteria:** clinically relevant systemic disease; pregnancy in the last 3 months; BMI >26.7 kg/m^2; previous OHSS; previous IVF failure due to poor response; abnormal bleeding from reproductive tract; active substance abuse **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 54) **Arm 2:** long agonist plus uFSH (n = 57) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** vaginal progesteron
Outcomes	**Outcomes reported:** live birth; mul ipl pregnancy; miscarriage; ectopic pregnancy; cancellation; oocyte number **Outcomes included in the me analysis:** live birth; multiple pregnancy; miscarriage; ectopic pregnancy; cancellation; oocyte numbe
Notes	**Type of publication:** publish d f ll-text manuscript **Trial registration:** unsta ed **Registration da e:** - **Conflict f i teres declaration:** unstated **Fund g:** "S pported by a grant from Serono Canada." **Author corr spondence:** none undertaken (author contact details not found) **Ca culations used to obtain absolute event numbers:** no **Inclus n in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Add ional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list.
Allocation concealment (selection bias)	Low risk	SNOSE.

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Miron 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Three cycles cancelled in the hMG group and four in the FSH group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010 Sele tive re orting not detected.
Other bias	Low risk	Trial conducted pre-2010 Multic ntre s dy. No concerns regarding validity of results. Effect size difference lower an two-fold between trial arms. No other biases detected.

Moffat 2021

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Switzerland **Language:** English **Setting:** single centre **Recruitment perio :** Augus 2013 to November 2017 **Sample size (to al randomised):** 114
Participants	**Inclusi n cri ria:** a least two of the following criteria: age ≥40 years; any risk factor for poor ovarian response; istory of severe pelvic infection; presence of ovarian endometriomas; previous ovarian surgery; previous chemotherapy; short menstrual cycles (<26 days); previous low ovarian response; abnormal ova an reserve tests (AFC ≤7, AMH ≤1.1 ng/ml) **Ex lusion criteria:** unstated **Pred ted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus clomifene citrate & hMG (n = 57) - two arms merged (see additional comments) **Arm 2:** short antagonist plus hMG (n = 57) - two arms merged (see additional comments)

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Moffat 2021 *(Continued)*

	Fertilisation method: IVF or ICSI **Embryo age at the time of transfer:** blastocyst (day 5+) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; miscarriage; oocyte number; blastocyst number **Outcomes included in the meta-analysis:** live birth; miscarriage; oocyte number; blastocyst number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT01577472 **Registration date:** 13 April 2012 **Conflict of interest declaration:** none declared **Funding:** "The costs for the HMG used for ovarian stim lation w re provided by IBSA Switzerland. The Study was also supported by the Repronatal Foundation, Ba el, Switzerland." **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** A total of 114 partic pants ere randomised to one of four groups: A) clomifene citrate with 450 IU of hMG (n =28); B) clomifene citrate with 150 IU of hMG (n = 29); C) placebo with 450 IU of hMG (n = 30); and D) placeb with 150 IU of hMG (n = 27). For the purposes of meta-analysis, groups A and B were amalgamated, and groups C and D were also merged.

Risk of bias

Bias	Authors' judgement	Suppo t for judgement
Random sequence generation (selection bias)	Low risk	computer-generated randomisation schedule in blocks of eight was provided b the hospital pharmacy".
Allocation concealment (selection bias)	Low risk	Centrally managed.
Blinding of participants and personnel (performance bias) All outcomes	Low ris	"Treating physicians were informed about the HMG starting dose but were blinded for the content of the capsules.", "double-blinded" trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Treating physicians were informed about the HMG starting dose but were blinded for the content of the capsules.", "double-blinded" trial.
Incomplete out ome data (attrition bias) All outcomes	Low risk	Five women cancelled (1 from group A; 1 from group B; and 3 from group C). ITT analysis not strictly performed but possible to extract absolute event numbers. Attrition rate <10%.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

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Mohamed 2006

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** January 2001 to December 2004 **Sample size (total randomised):** 257
Participants	**Inclusion criteria:** age>39 years; nulliparous women; FSH ≤10 IU/ml; oestradiol ≤60 ng/ml **Exclusion criteria:** PCOS **Predicted response as stated by the trialists:** p edicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** yes (≥35 years) **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n 129) **Arm 2:** long agonist plus uFSH (= 128) **Fertilisation method** u stated **Embryo age at the ime of t ansfer:** cleavage stage (days 2-4) **Luteal phase support:** intramuscular progesterone
Outcomes	**Outc mes reported:** miscarriage; oocyte number **Outcomes ncluded in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial gistration:** unstated **Regi tration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - marcandrea@hotmail.com (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported) **Additional comments:** -

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Mohamed 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization number sequence".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes repo ted.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Se en women cancelled in the rFSH group and 9 in the uFSH group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted a d publ shed pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No conce ns ega ing validity of results. Effect size difference lower than two-fold b twee tria arms. No other biases detected.

Mohamed 2006a

Study characteristics

Methods	**Design:** n omised controlled trial **Coun ry:** Un ed Kingdom **Language:** nglish **Se ting:** single centre **Recru tment period:** unstated **Sample size (total randomised):** 30
Participants	**Inclusion criteria:** known low-responding women (<6 follicles >12 mm in previous IVF cycle) **Exclusion criteria:** FSH >13 IU/l; previous hormonal therapy **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no

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Mohamed 2006a *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** agonist flare plus hMG (n = 15) **Arm 2:** short antagonist plus hMG (n = 15) **Fertilisation method:** unstated **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - kamel.mohamed@ntlworld.com (23 February 2022) **Calculations used to obtain absolute ev nt numbers:** no **Inclusion in meta-analysis:** no (u clea risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	**Authors' judgemen**	**upport for judgement**
Random sequence generation (selection bias)	Unclear risk	The patients (…) were randomized on site using sealed envelopes".
Allocation concealment (selection bias)	Uncl r risk	"sealed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Un lear risk	Unstated, subjective outcomes reported (e.g., cancellation).
Blinding of outcome assessment (detec ion bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., cancellation).
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not performed. Attrition >10% in the antagonist arm.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.

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Mohamed 2006a *(Continued)*

Other bias	Unclear risk	Trial conducted pre-2010. Timeline unclear.

Mohsen 2013

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Egypt **Language:** English **Setting:** single centre **Recruitment period:** April 2010 to January 2012 **Sample size (total randomised):** 60
Participants	**Inclusion criteria:** regular menstrual cycles; BMI < 0 kg/m^2 ≥1 failed IVF cycles **Exclusion criteria:** severe endometriosis; history of previous pelvic or ovarian surgery; clinically significant systemic disease; endocrine or metabolic disorders; severe male factor **Predicted response as stated by the triali ts:** p dicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian r serve **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity)**
Interventions	**Arm 1:** short antago i t plus letrozole & hMG (n = 30) **Arm 2:** agonist fla e plus hMG (n = 30) **Fertil sation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Lut al phase support:** vaginal progesterone
Outcomes	**Outc mes reported:** clinical pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - imankhalil3@hotmail.com (16 September 2021) **Calculations used to obtain absolute event numbers:** no

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Mohsen 2013 *(Continued)*

Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated random numbers".
Allocation concealment (selection bias)	Unclear risk	"each patient chose a sealed envelope ontaining e randomized assignment to either one of the two protocols", unclea if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outco es reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed S x women cancelled in the short antagonist group, and five in the agonist flare group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conduc ed post-2010. Registration details unstated. Selective reporting not de cted
Other bias	Unclear risk	Trial conducted post-2010. Registration details unstated. Single centre study with pla sible recruitment rates. Effect size difference lower than two-fold between trial arms.

Moini 2019

Study characteristics

Methods	**Design:** randomised controlled trial **C untry:** Iran **La guage:** English **Sett ng:** single centre **Recruitment period:** February to September 2017 **Sample size (total randomised):** 160
Participants	**Inclusion criteria:** low-responding women (Bologna criteria) **Exclusion criteria:** POI; donor/recipient treatments; metabolic or endocrine disorders including hyperprolactinaemia and hypo/hyperthyroidism; endometriosis; BMI >30 kg/m^2; azoospermia in the male partner **Predicted response as stated by the trialists:** predicted low response

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Moini 2019 *(Continued)*

	Oocyte donors: no
	Cause of infertility: low ovarian reserve
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus letrozole & rFSH & hMG (n = 80)
	Arm 2: short antagonist plus rFSH & hMG (n = 80)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; oocyte umber
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text man script
	Trial registration: IRCT201701291952N8
	Registration date: 19 September 2017
	Conflict of interest declaration: one declared
	Funding: unstated
	Author correspondence: non unde taken
	Calculations used to obtain abs lute event numbers: no
	Inclusion in meta-analysis no (high risk of other biases; primary review outcomes not reported)
	Additional comments:

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"block randomization with blocks number six was conducted by statistics advisor using STATA software".
Allocation concealment (selection bias)	Lo risk	"Only the statistics advisor was informed regarding the random allocation list of patients".
Blinding of parti ipants and personnel (pe fo mance bias) All outcomes	Low risk	"double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind".
Incomplete outcome data (attrition bias)	Low risk	ITT analysis performed. No loss to follow-up.

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Moini 2019 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Retrospectively registered. Selective reporting not detected.
Other bias	High risk	Trial conducted post-2010 and retrospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Mokhtar 2015

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** 2012 to 2014 **Sample size (total randomised):** 150
Participants	**Inclusion criteria:** age 20-38 years; PCOS; normal prolactin and thyroid function; normal cardiac, hepatic and renal functions who had normal pontaneous onset of puberty and normal sexual development **Exclusion criteria:** FSH>12 or ≥2 A T failure or ≥2 first trimester abortions; ovarian cyst; anatomical uterine, cervical or tubal anom ly **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertil ty:** PCOS **Subgroup (age):** no **Subgro p (MI):** no **Subgroup (ethnicity):** no
Interventions	**Ar 1:** long agonist plus rFSH (n = 50) **Arm 2:** short antagonist plus rFSH (n = 100) - two arms merged (see additional comments) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; multiple pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** IRCT2012120311653N1

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Mokhtar 2015 *(Continued)*

Registration date: 16 July 2013

Conflict of interest declaration: none declared

Funding: unstated

Author correspondence: yes - af85af@yahoo.com, eftekhar@ssu.ac.ir (16 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias, high risk of other biases; primary review outcomes not reported)

Additional comments: Women with PCOS undergoing COS were ra domis d to one of three groups: GnRH agonist (long, n = 50), GnRH antagonist (short flexible, n = 5) and GnRH antagonist (short fixed, n = 50). For the purposes of meta-analysis, we planned to amalgamat both gr ups in which a short antagonist was administered (n = 100).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated random letters".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, ubjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event values. Six women cancelled in the GnRH agonist group and six in the GnRH antagonist groups (total = 12). Attrition >10% in the GnRH agonist group.
Selective reporting (reporting bias)	High ris	Trial conducted post-2010. Retrospectively registered.
Other bias	High risk	Trial conducted post-2010 and retrospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Mollo 2005

Study characteristics

Methods

Design: randomised controlled trial

Country: Italy

Language: English

Setting: single centre

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Mollo 2005 *(Continued)*

	Recruitment period: unstated
	Sample size (total randomised): 116
Participants	**Inclusion criteria:** age >37 years; risk of low ovarian response; basal FSH >9 IU/l
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: predicted low response
	Oocyte donors: no
	Cause of infertility: low ovarian reserve
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH & uhCG (n = 58
	Arm 2: agonist flare plus rFSH & uhCG (n = 58)
	Fertilisation method: unstated
	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** oocyte number
	Outcomes included in the meta-an lysis: none
Notes	**Type of publication:** conferen e abstract
	Trial registration: unstated
	Registration date:
	Conflict of interest declaration: unstated
	Funding: uns ated
	Author cor espondence: none undertaken (author contact details not found)
	Calculations used to obtain absolute event numbers: no
	In lusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)
	Add ional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised into two groups", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.

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Mollo 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis unclear. Loss to follow-up unstate
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010 Sele tive re orting not detected.
Other bias	Unclear risk	Trial conducted pre-2010 S ngle entre tudy. Recruitment rates unclear as study timeline unstated Effect size ifference lower than two-fold between trial arms. No other biases etected.

Moraloglu 2008

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Turkey **Language:** English **Setting:** single centre **Recruitment perio :** Ma 2005 to August 2006 **Sample size (to al randomised):** 93
Participants	**Inclusi n cri ria:** ag 25-38 years **Exclus n c iteria:** age >38 years; BMI ≥30 kg/m^2; previous low response (<4 follicles and/or serum oestradiol vel <500 pg/ml on the day of hCG); >3 previous IVF cycles; PCOS; basal serum FSH ≥10 IU/ml; systemic disease; severe endometriosis or uterine/ovarian abnormalities **P dicted response as stated by the trialists:** predicted normal response **Oo yte donors:** no **Cau e of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 45) **Arm 2:** long agonist plus rFSH (n = 48) **Fertilisation method:** IVF or ICSI

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Moraloglu 2008 *(Continued)*

	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; cancellation; oocyte number
	Outcomes included in the meta-analysis: OHSS
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - sevtapkilic@gmail.co (16 Sep mber 2021)
	Calculations used to obtain absolute event nu bers: no
	Inclusion in meta-analysis: yes (sensitivity analysi includ ng all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support f r ju gement
Random sequence generation (selection bias)	Low risk	"computer gene ated randomisation scheduled".
Allocation concealment (selection bias)	Unclear risk	ssigned via numbered sealed envelopes", although unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"op n-label", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open-label", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Three cycles cancelled in group 1 and two in group 2. Attrition <10% in both trial arms.
Selective reporti g (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Morgia 2004

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** January 2000 to July 2002 **Sample size (total randomised):** 129
Participants	**Inclusion criteria:** age <43 years; previous IVF cycle with low ovarian r sponse **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted w response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** natural cycle IVF (n = 59) **Arm 2:** agonist flare plus uFSH (n = 70) **Fertilisation method:** ICSI **Embryo age at the tim of transfer:** cleavage stage (days 2-4) **Luteal phase support:** ntramuscular progesterone
Outcomes	**Outcomes repor ed:** miscarriage; cancellation **Outcomes in uded in the meta-analysis:** none
Notes	**Type of pu lication:** published full-text manuscript **Tr al registration:** unstated **Regi tration date:** - **Con ict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - marcandrea@hotmail.com (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported) **Additional comments:** -
Risk of bias	

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Morgia 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated number sequence".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes r ported
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. o loss to fo low-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre 2010. Single centre study with plausible recruitment rates. No concerns regard validity of results. Effect size difference lower than two-fold between tr al arms. No other biases detected.

Muhammad 2019

Study characteristics	
Methods	**Design:** randomised c ntrol ed trial **Country:** I aq **Lang age:** English **Setting:** s gle centre **Re ruitment period:** July 2018 to May 2019 **Sample size (total randomised):** 114
Participants	**Inclusion criteria:** low ovarian response **Exclusion criteria:** age <18 or >43 years; BMI >30 kg/m^2; severe endometriosis; POI; thyroid dysfunction; hyperprolactinaemia **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no

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Muhammad 2019 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** agonist flare plus rFSH & hMG (n = 76) - two arms merged (see additional comments) **Arm 2:** short antagonist plus rFSH & hMG (n = 38) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - fmjafalizzi@y hoo co.uk (15 September 2021) **Calculations used to obtain absolute ev nt numbers:** yes **Inclusion in meta-analysis:** no (u clea risk of selection and other biases; primary review outcomes not reported) **Additional comments:** A tot l of 1 4 women were randomised to undergo either 1) micro-dose flare up (n = 38); 2) standard dose fl re up (n = 38); or 3) short antagonist protocol (n = 38). For the purposes of meta-analysis, we pla ed to malgamate groups 1 and 2.

Risk of bias

Bias	Authors' judgement	upport for judgement
Random sequence generation (selection bias)	Unclea risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Uncle r risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection b s) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers from percentages. Total of 27 cancellations in groups 1 and 2, and 16 in group 3 (total = 43). Attrition >10%.

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Muhammad 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration timeline unstated. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted post-2010. Registration status unspecified. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Mukherjee 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** India **Language:** English **Setting:** single centre **Recruitment period:** January 2009 to December 2010 **Sample size (total randomised):** 94
Participants	**Inclusion criteria:** age 25-35 years; normal t yroid function and serum prolactin levels; no PCOS; no endometriosis; unexplained infertility; male pa tner with azoospermia **Exclusion criteria:** unstated **Predicted response as stated y the ialists:** unstated **Oocyte donors:** no **Cause of infertility:** male factor **Subgroup (age):** no **Subgroup (BMI)** no **Subgroup (et nicity)** no
Interventions	**Arm 1:** s o t antagonist plus letrozole & rFSH (n = 42) **Arm 2:** short antagonist plus rFSH (n = 52) **Fe ilisation method:** ICSI **Em ryo age at the time of transfer:** cleavage stage (days 2-4) **Lut al phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; multiple pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared

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Mukherjee 2012 *(Continued)*

Funding: none sought

Author correspondence: yes - shiuli.mukherjee@gmail.com (15 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized by sealed envelopes".
Allocation concealment (selection bias)	Unclear risk	"randomized by sealed e velopes , unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single blind trial, subjective utcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT ana ysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	T ial conducted up to 2010. Registration status unstated.
Other bias	Low risk	Trial conducted up to 2010. Registration status unstated. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Musters 2012

Study characteristics

Methods	**Des gn:** randomised controlled trial **Country:** The Netherlands **Language:** English **Setting:** multicentre **Recruitment period:** August 2008 to April 2010 **Sample size (total randomised):** 244
Participants	**Inclusion criteria:** age 35–41 years or <35 years with FSH level <12 IU/ml accompanied by AFC ≤5

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Musters 2012 *(Continued)*

	Exclusion criteria: endocrine disease; Cushing syndrome; adrenal hyperplasia; hyperprolactinaemia; acromegaly; hypothalamic amenorrhea; hypothyroidism; Diabetes Mellitus type I; PCOS **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 116) **Arm 2:** long agonist plus rFSH (n = 128) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stag (days 2 4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** clinical pregnancy; going pregnancy; miscarriage; cancellation **Outcomes included in the meta-analys s:** cli ical pregnancy; ongoing pregnancy; miscarriage; cancellation
Notes	**Type of publication:** published ful text manuscript **Trial registration:** EudraCT umbe 2007-007487-22 **Registration date:** 24 September 2008 **Conflict of interest ecl ation:** unstated **Funding:** "The autho thank Merck Serono for the donation of the rLH (Luveris) and the HCG (Ovitrelle)." **Author corre pondence:** none undertaken **Calcula ions used to obtain absolute event numbers:** no **Inclusion in m ta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	thors' judgement	Support for judgement
Random sequence g nera-tion (selection bias)	Low risk	"Central web-based randomization (…) using a computer program minimization procedure with stratification according to study centre".
Allocation concealment (selection bias)	Low risk	"Central".
Blinding of participants and personnel (performance bias)	High risk	"The study was not blinded for patients and doctors, but the embryologists and IVF technicians who evaluated the primary outcome of the study, i.e. embryo quality, were

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Musters 2012 *(Continued)*

All outcomes		unaware of treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	High risk	"The study was not blinded for patients and doctors, but the embryologists and IVF technicians who evaluated the primary outcome of the study, i.e. embryo quality, were unaware of treatment allocation.". Subjective outcomes (e.g. cancellation) also reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Ten women were cancelled in the rFSH/rLH group, and fifteen in the rFSH group. Attrition >10% in the rFSH group.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken within six months of recruitment commencement. No evidence of elective reporting.
Other bias	Low risk	Trial conducted post-2010 and registered within six months of commencement. Multicentre study. Effect size difference lower than two-fold between trial arms.

Nabati 2016

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** January 20 2 to January 2013 **Sample size (total andom ed):** 123
Participants	**Inclusion criteri :** low-responding women **Exclus on cri ria:** history of endometriosis; sustained hyperprolactinaemia or other hormonal disorders; aving single ovary; FSH >11 mIU/l; male azoospermia **Predicted r sponse as stated by the trialists:** predicted low response **O cyte donors:** no **Caus of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus rFSH (n = 61) **Arm 2:** short antagonist plus letrozole & rFSH (n = 62) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** pronuclear (day 0-1)

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Nabati 2016 *(Continued)*

	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** IRCT2014050516858N3 **Registration date:** 6 February 2015 **Conflict of interest declaration:** none declared **Funding:** "This study was supported by a grant from Mazandaran U iversity o medical sciences, sari, Iran." **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of se ection bias high risk of other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgeme t
Random sequence generation (selection bias)	Unclear risk	Unstated
Allocation concealment (selection bias)	Unclear risk	Unsta d.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Uns ated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Uncl r risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Hi h risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Eleven women cancelled in the agonist flare protocol and twenty-four in the letrozole/rFSH protocol. Attrition >10% in both trial arms.
Selective reportin (reporting bias)	High risk	Trial conducted post-2010. Retrospectively registered.
Other bias	High risk	Trial conducted post-2010 and retrospectively registered. Single centre study with plausible recruitment rates. Effect size difference higher than two-fold between trial arms.

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Nagulapally 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** India **Language:** English **Setting:** single centre **Recruitment period:** December 2009 to September 2011 **Sample size (total randomised):** 40
Participants	**Inclusion criteria:** tubal factor infertility **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** un tated **Oocyte donors:** no **Cause of infertility:** tubal **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus clom fene cit te & hMG (n = 20) **Arm 2:** short antagonist plus letr zole & hMG (n = 20) **Fertilisation method:** unstated **Embryo age at the tim of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes repor ed:** OHSS; cancellation; oocyte number; number of embryos cryopreserved **Outcomes in uded in the meta-analysis:** OHSS
Notes	**Type of pu lication:** conference abstract **Tr al registration:** unstated **Regi tration date:** - **Con ict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not found) **Calculations used to obtain absolute event numbers:** yes **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -
Risk of bias	

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Nagulapally 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed b t possible to extract absolute event numbers from percentages. Attrition rate 10% in both trial arms. Four women were cancelled in the clom fene gro p, and six in the letrozole group (total = 10).
Selective reporting (reporting bias)	Low risk	Trial conducted and p blished pre-2010. Selective reporting not detected.
Other bias	High risk	Trial conducted pre 2 10. Single centre study with plausible recruitment rates. No concer s regarding validity of results. Effect size difference higher than two-fold etween rial arms (e.g. pregnancy rate). No other biases detected.

Nakagawa 2007

Study characteristics	
Methods	**Design:** random sed controlled trial **Countr :** Jap n **Langu ge:** English **Setting:** single centre **Recruitment period:** October 2005 to June 2006 **S mple size (total randomised):** 86
Participants	**Inclusion criteria:** unstated **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no

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Nakagawa 2007 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 53) **Arm 2:** long agonist plus hMG (n = 33) **Fertilisation method:** unstated **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** miscarriage; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - nakagawa j@ncchd.go.jp (16 September 2021) **Calculations used to obtain absolute ev nt numbers:** no **Inclusion in meta-analysis:** no (u clea risk of selection bias; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclea risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detecti n bias) All outcomes	Low isk	Unstated, however only objective outcomes reported.
Incomplete outcome d ta (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers from percentages. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Nakagawa 2007 *(Continued)*

Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Nardo 2000

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 110
Participants	**Inclusion criteria:** primary infertility lasting 2 12 years; previous <3 cycles of ART **Exclusion criteria:** unstated **Predicted response as stated by the t alists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicit):** no
Interventions	**Arm 1:** long agonist plus FSH (n = 75) **Arm 2:** long a onist plus uFSH (n = 35) **Fertili atio method:** unstated **Embryo age the time of transfer:** unstated **Lu eal phase support:** intramuscular and vaginal progesterone
Outcomes	**O tcomes reported:** live birth; OHSS; oocyte number **Out omes included in the meta-analysis:** live birth; OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not found)

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Nardo 2000 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes (OHSS) reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Assessor-blind study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Absolute numbers av lable for ITT analysis. Two cycles cancelled in the rFSH group, and 3 in the uFSH group (total = 5). Attrition <10%.
Selective reporting (reporting bias)	Low risk	Tria conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial a ms. No other biases detected.

Nassar 2001

Study characteristics

Methods	**D sign:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** single centre **Recruitment period:** January 2000 to October 2000 **Sample size (total randomised):** 121
Participants	**Inclusion criteria:** age <36 years **Exclusion criteria:** PCOS; BMI <35 kg/m^2; severe endometriosis; low response in previous stimulation cycles; >2 IVF failures; previous OHSS; male azoospermia **Predicted response as stated by the trialists:** unstated

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Nassar 2001 *(Continued)*

	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 61)
	Arm 2: long agonist plus rFSH & hMG (n = 60)
	Fertilisation method: unstated
	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** clinical pregnancy; ongoing pregnancy; cancellation; oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** conference abstract
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: nstated
	Funding: unstated
	Author correspondence: non unde taken (author contact details not found)
	Calculations used to obtain abs lute event numbers: no
	Inclusion in meta-analysis no (unclear risk of selection bias; primary review outcomes not reported)
	Additional comments:

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Un lear risk	Unstated.
Allocation concealment (selection bias)	Un lear risk	Unstated.
Blinding of parti ipants and personnel (pe fo mance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias)	Unclear risk	Unstated.

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Nassar 2001 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

NCT00257556 2010

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** International (Germany and United Kingdom) **Language:** English **Setting:** multicentre **Recruitment period:** October 2005 to April 2009 **Sample size (total randomised):** 80
Participants	**Inclusion criteria:** age 20-35 years; BM 18-32 kg/m^2; normal endocrine assessment within the last six months; normal pelvic ultrasound (two ovaries, no ovarian abnormalities and normal uterus) within the last six months; ≤2 previous ART cycles regular menstrual cycles (24-35 days); no fertility treatment within the three months preced g enrolment; tubal factor or unexplained infertility; normal SFA (WHO criteria); negative urine pregnancy t st; clinically normal baseline haematology, clinical chemistry, and urinalysis parameter values; negative serum HBsAg and HIV antibody tests; screening endocrine test results (estradiol, LH, FSH, prog terone, prolactin, TSH) in early follicular phase within the normal limits for the clinical laboratory **Exclusion criteria:** presence of any clinically relevant systemic disease (e.g., insulin-dependent diabetes mellitus); history o or current endocrine disease, including PCOS and hyperprolactinaemia; history of coa ulatio disorders; persistent ovarian cysts; contraindications for the use of gonadotrophins or GnRH anta onists; history of hypersensitivity to any of the constituents of the study medication or related compounds; ≥3 previous cycles of IVF (or other ART); history of alcohol abuse (>30 units per week on a r gular basis); history of chemo- or radiotherapy; currently breast-feeding, pregnant or with a contraind ation to pregnancy; diagnosed low response in prior IVF treatment; previous severe OHSS during COS; investigational drug within the 30 days prior to treatment; any other condition or history that the investigator considers might increase the risk to the individual **Predic ed response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus hMG (n = 38) **Arm 2:** short antagonist plus rFSH (n = 42)

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NCT00257556 2010 *(Continued)*

	Fertilisation method: unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** OHSS; miscarriage; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** trial registration **Trial registration:** NCT00257556 or EUCTR2004-001307-35-GB **Registration date:** 23 November 2005 **Conflict of interest declaration:** unstated **Funding:** Ferring pharmaceuticals **Author correspondence:** yes - DK0-Disclosure@ rring.com 5 September 2021) **Calculations used to obtain absolute event numb rs:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support f judg ment
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open-label trial", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label trial", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Forteen women in the hMG group and ten women in the rFSH group did not complete the trial. Attrition >10% in both trial arms.
Selective reporting (- porting bias)	Low risk	Trial conducted post-2010. Registration undertaken within six months of recruitment commencement. No evidence of selective reporting.
Other bias	Low risk	Trial conducted post-2010 and registered within six months of commencing recruitment. Multicentre study. Effect size difference lower than two-fold between trial arms.

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Neveu 1987

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** France **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 20
Participants	**Inclusion criteria:** age 28-38 years; tubal infertility; normal ovulation; ormal prolactin and androgen levels **Exclusion criteria:** unexplained infertility with or without endometriosis; POI; pelvic adhesions; male infertility **Predicted response as stated by the trialists:** u stated **Oocyte donors:** no **Cause of infertility:** tubal **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** uFSH without pituita y suppression (n = 10) **Arm 2:** long agonist plus uFSH (= 10) **Fertilisation method** u stated **Embryo age at the ime of t ansfer:** unstated **Luteal phase support:** hCG
Outcomes	**Outc mes reported:** clinical pregnancy; oocyte number **Outcomes ncluded in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial gistration:** unstated **Regi tration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not found) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

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Neveu 1987 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes repo ted.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Two cycles were cancelled in the uFSH-only group (20%) and no cycles were cancelled in the agonist plus uFSH group.
Selective reporting (reporting bias)	Low risk	Trial conducted a d publ shed pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study tim lin uns ated. Effect size difference lower than two-fold between trial arms No the biases detected.

Ng 2001

Study characteristics

Methods	**Design:** n omised controlled trial **Coun ry:** Chi a **Language:** nglish **Se ting:** single centre **Recru tment period:** January to September 1999 **Sample size (total randomised):** 40
Participants	**Inclusion criteria:** age <40 years; day 2 serum FSH <10 IU/l; regular ovulatory cycles; long protocol of pituitary downregulation; ICSI indicated for severe male factor **Exclusion criteria:** previous ovarian cystectomy or oophorectomy; short GnRH antagonist for pituitary downregulation; smoking; previous failed ICSI; surgical sperm retrieval **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no

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Ng 2001 *(Continued)*

	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 20)
	Arm 2: long agonist plus rFSH (n = 20)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: hCG
Outcomes	**Outcomes reported:** ongoing pregnancy; multiple pregnancy
	Outcomes included in the meta-analysis: ongoing pregnancy; mu tiple pregnancy
Notes	**Type of publication:** published full-text manuscrip
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none undertak
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)
	Additional comments: -

Risk of bias

Bias	Authors' judgemen	Support for judgement
Random sequence genera-tion (selection bias)	Low risk	"Computer-generated list of random number".
Allocation concealment (selection bias)	Low risk	Numbers placed in "sealed envelopes" by an external practitioner.
Blinding of participants and personnel (perfor-mance bias) All outcomes	Low risk	Embryologists blinded. Only objective outcomes reported.
Blinding of outcome as sessment (detect on b as) All outcomes	Low risk	Embryologists blinded. Only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (re-porting bias)	Low risk	Selective reporting not detected.

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Ng 2001 *(Continued)*

Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Nyboe Andersen 2005

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** international **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 731
Participants	**Inclusion criteria:** age 21-37 years **Exclusion criteria:** unstated **Predicted response as stated by the t alists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicit):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 363) **Arm 2:** long a onist plus rFSH (n = 368) **Fertili atio method:** unstated **Embryo age the time of transfer:** unstated **Lu eal phase support:** unstated
Outcomes	**O tcomes reported:** embryo quality; ongoing pregnancy; oocyte number **Out omes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken

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Nyboe Andersen 2005 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (insufficient data in the abstract; author contact details not found)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"open-label, assessor-blind", howev r only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"open-label, assessor-blind", however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed. Attrition unstated.
Selective reporting (reporting bias)	Low risk	Select ve reporting not detected.
Other bias	Low risk	N evid nce of other biases.

Nyboe Andersen 2008

Study characteristics

Methods	**Design:** ra domised controlled trial **Co ntry:** International (Denmark, Finland, Norway and Sweden) **Language:** English **Set ng:** multicentre **R cruitment period:** August 2003 to November 2004 **Sample size (total randomised):** 526
Participants	**Inclusion criteria:** age <40 years; indication for IVF or ICSI; first, second or third cycle; regular menstrual cycle defined as bleeding intervals between 21 and 35 days **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no

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Nyboe Andersen 2008 *(Continued)*

	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 261)
	Arm 2: long agonist plus rFSH & rLH (n = 265)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; ongoing preg ncy; multiple pregnancy; miscarriage; cancellation; oocyte number; number of embryos cryop eserved
	Outcomes included in the meta-analysis: clinical pregnanc ; ongoing pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number; numb r of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript
	Trial registration: KF02-035/03
	Registration date: 4 November 2007
	Conflict of interest declaration: nstated
	Funding: unstated
	Author correspondence: yes anyboea@rh.hosp.dk (16 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)
	Additional comments:

Risk of bias

Bias	Authors j dgement	Support for judgement
Random sequence generation (selection bias)	Lo risk	"Random blocks".
Allocation concealment (selection bias)	Low risk	SNOSE.
Blinding of part ipant and personnel (per - mance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias)	Low risk	ITT analysis performed. Attrition rate similar (15 cancelled cycles in each arm), <10%.

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Nyboe Andersen 2008 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Ob'edkova 2021

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Russia **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 51
Participants	**Inclusion criteria:** age 35-41 years; BM 17.5-30 mg/m^2; predicted low response; serum FSH <15 IU/l **Exclusion criteria:** contraindicati n to fert lity treatment; chromosomal abnormalities; recurrent pregnancy loss; severe male factor (g., az spermia) **Predicted response as stated by the trialists:** low **Oocyte donors:** no **Cause of infertility** unstate **Subgroup (age):** no **Subgroup (B I):** no **Subgr up (thnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 25) **A 2:** short antagonist plus hMG (n = 26) **Fe ilisation method:** IVF **Embryo age at the time of transfer:** days 4-5 post-fertilisation **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** cancellation **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** unstated

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Ob'edkova 2021 *(Continued)*

Conflict of interest declaration: none declared

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Author correspondence: yes, obedkova_ks@mail.ru emailed on 12 July 2022, reply awaited.

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk risk of selection and other biases, primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"envelope technique".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, howeve only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	To l number of cancelled cycles 9/51 (17.65%). ITT analysis not clearly reported.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Uncl r risk	Single centre study, recruitment timeline unstated. Trial published in 2021, registration unclear.

Olivennes 2000

Study characteristi s

Methods	**Design:** randomised controlled trial **Country:** France **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 154

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Olivennes 2000 *(Continued)*

Participants	**Inclusion criteria:** age 18-39 years; COS for IVF or ICSI; normal menstrual cycles (24-35 days); FSH ≤10 IU/l; normal uterus; ≤3 previous IVF-ET attempts **Exclusion criteria:** PCOS; severe endometriosis **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus hMG (n = 115) **Arm 2:** long agonist plus hMG (n = 39) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** unstated **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnan y; ongoing pregnancy; miscarriage; ectopic pregnancy; oocyte number **Outcomes included in the meta- nalysis** OHSS
Notes	**Type of publication:** published f ll-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest de lara ion:** unstated **Funding:** unsta d **Autho corre pondence:** none undertaken (author contact details not found) **Calculat s used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary ou comes [live birth and/or OHSS]) **Additi nal comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence gener tion (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.

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Olivennes 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study. High risk of bias due to reporting subjective outcomes such as OHSS.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study. High risk of bias due to reporting subjective outcomes such as OHSS.
Incomplete outcome data (attrition bias) All outcomes	High risk	Absolute numbers for OHSS rate calculated from table percentages, therefore prone to error as number analysed diferred from umber randomised. Two women cancelled in the cetrorelix group, and three in the triptorelin group. Attrition <10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. S lective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicent e study. No concerns regarding validity of results. Effect size difference lower t an two-fold between trial arms. No other biases detected.

Out 1995

Study characteristics	
Methods	**Design:** randomised controlled tr l **Country:** The Netherlands **Language:** English **Setting:** multicentre **Recruitment period** March 1992 to August 1993 **Sample size (to l randomised):** 1027
Participants	**Inclu ion criteria:** age 18-39 years; cause of infertility amenable to IVF; ≤3 previous IVF attempts; normo-ovu ato y cycles (24-35 days); good physical and mental health; body weight 80-130% of the ideal body weigh **Ex lusion criteria:** endocrine abnormalities such as hyperprolactinaemia; PCOS; absence of ovarian fu ction; ovarian and/or abdominal abnormalities; hypertension; chronic cardiovascular, hepatic, renal or pulmonary disease; history of current abuse of alcohol or drugs (within 12 months); non-registered investigational drugs within 3 months prior to screening; male infertility **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 615)

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Out 1995 *(Continued)*

	Arm 2: long agonist plus uFSH (n = 412) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** hCG or progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; ongoing pregnancy; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (autho contact details not found) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support fo judgement
Random sequence generation (selection bias)	Low risk	"Randomization list used with patient boxes in which the mediation was kept."
Allocation concealment (selection bias)	Unclear risk	Subjects received a "subject number from a randomization list".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Assessor-blind study".
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. A total of 152 patients (85 in the rFSH group and 67 in the uFSH group) started treatment but did not undergo embryo transfer, therefore attrition >10% in both groups.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Ozmen 2009

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Turkey **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 70
Participants	**Inclusion criteria:** second cycle of ICSI after previous low r ponse (defined as having at least one of the following criteria in a previous COS cycle: cycle ca llation due to low oestradiol concentrations on day 6 of the cycle (<130 pg/ml) or on the day of human chorionic gonadotrophin (HCG) administration(<450 pg/ml); or <4 retrieved oocytes **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus letrozole & rFSH (n = 35) **Arm 2:** short antagonist plus rFSH (n = 35) **Fertilisation me hod:** ICSI **Embry age a the ti e of transfer:** cleavage stage (days 2-4) **Luteal ha e support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number; number of cleavage-stage embryos **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - batuhanozmen@gmail.com (16 September 2021) **Calculations used to obtain absolute event numbers:** no

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Ozmen 2009 *(Continued)*

Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes", but unclear if SNOSE
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outco es reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not str ctly performed but possible to extract absolute event numbers. Four cycl s wer cancelled in group A, and 10 in group B (total = 14). Attrition rate >10%.
Selective reporting (reporting bias)	Low risk	Trial conduc ed a d published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study with unclear recruitment rates. Effe t si difference lower than two-fold between trial arms. No other biases detected.

Pabuccu 2007

Study characteristics

Methods

Design: randomised controlled trial

C untry: Turkey

La guage: English

Sett ng: single centre

Recruitment period: November 2002 to February 2006

Sample size (total randomised): 246

Participants

Inclusion criteria: endometriosis; normal uterine cavity by either hysterosalpingography or hysteroscopy <1 year before the study

Exclusion criteria: hydrosalpinx; documented tuberculosis; thaw cycles; male factor infertility

Predicted response as stated by the trialists: unstated

Oocyte donors: no

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Pabuccu 2007 *(Continued)*

	Cause of infertility: endometriosis
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 124)
	Arm 2: long agonist plus rFSH (n = 122)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: various
	Luteal phase support: micronised vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; miscarriage; cyte n mber
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes gogse onalan@yahoo.com (16 September 2021)
	Calculations used to obtain bsolut event numbers: no
	Inclusion in meta-analysis: no nclear risk of selection bias [allocation concealment unstated]; primary review outcom s no reported)
	Additional commen s -

Risk of bias

Bias	Auth rs' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list.
Allocation concealment (selection bias)	Uncle r risk	Unstated.
Blinding of partic pants and personnel (erformance bias) All outcomes	w risk	Unstated, however only objective outcomes reported for the purpose of meta-analysis.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported for the purpose of meta-analysis.

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Pabuccu 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis not strictly performed but possible to extract absolute event numbers. After randomisation, a total of 20 cases were cancelled due to insufficient ovarian response (unstated how many from each group).
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detec ed.

Pacchiarotti 2007

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** unstated **Recruitment period:** June 2005 to March 2006 **Sample size (total randomised):** 119
Participants	**Inclusion criteria:** age 27-38 years; ubal factor, male factor or unexplained infertility; normal serum FSH, LH, E2 and prolactin; regular vulatory cycles; normal uterine cavity; BMI 20-26 kg/m^2; first IVF treatment **Exclusion criteria:** previous low esponse; previous OHSS; PCOS; azoospermia in the male partner Clinical signs of infe tio de cted in semen analysis **Predicted response as stated by the trialists:** unstated **Oocyte dono s:** no **Cause f infertility:** various **Subgroup (ag):** no **Subgroup (BMI):** no **bgro p (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & uFSH (n = 58) **Arm 2:** long agonist plus rFSH (n = 61) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** miscarriage; cancellation; oocyte number **Outcomes included in the meta-analysis:** none

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Pacchiarotti 2007 *(Continued)*

Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - selmanha@yahoo.com (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias [alloc tion conc alment unstated]; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random assignment schedule".
Allocation concealment (selection bias)	Unclear risk	"Sealed and numbe ed envelopes", although unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open st dy" sub ective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open study", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers. One cycle cancelled in the u/rFSH group, and two in the rFSH group (total = 3). Attrition in both groups <10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Pacchiarotti 2010

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English

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Pacchiarotti 2010 *(Continued)*

	Setting: multicentre
	Recruitment period: July 2008 to September 2009
	Sample size (total randomised): 122
Participants	**Inclusion criteria:** tubal, idiopathic, or male factor infertility; serum FSH levels on day 3 of the ovarian cycle <12 IU/l; regular menstrual cycles; endogenous LH <1.2 IU/l; normal uterine cavity
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 60)
	Arm 2: long agonist plus rFSH & rLH (n = 62)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: cleavage tage (days 2-4)
	Luteal phase support: intramusc lar prog sterone
Outcomes	**Outcomes reported:** cancel ation; oocyte number
	Outcomes included in the met -analysis: none
Notes	**Type of publication** pub ished full-text manuscript
	Trial registratio : un tated
	Registrat date
	Conf ct of in erest declaration: none declared
	Funding: u stated
	Au hor correspondence: yes - arypac@alice.it (16 September 2021)
	Calculations used to obtain absolute event numbers: no
	Incl sion in meta-analysis: no (unclear risk of selection bias [allocation concealment unstated]; primar review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computering randomization".

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Pacchiarotti 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but po sible to ex act absolute event numbers. Two women lost to follow-up in group A, and ni e women lost to follow-up in group B (>10%).
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010 Selec e reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicent e study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Papanikolaou 2012

Study characteristics	
Methods	**Design:** randomised controll d trial **Country:** Greece **Language:** English **Setting:** single centr **Recruitm t peri d:** August 2007 to December 2009 **Samp e size otal randomised):** 190
Participants	**Inclusion cr teria:** age <39 years; FSH <12 mIU/ml; <3 previous IVF cycles **Exclusion criteria:** known endocrine disorders; endometriosis stages III and IV; cases where blood was drawn and analysed in another laboratory; ovarian stimulation cancellation if progesterone was >1.5 g/ml nd estradiol >80 pg/ml on the day of initiation of gonadotrophins **Pred cted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 96)

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Papanikolaou 2012 *(Continued)*

	Arm 2: long agonist plus rFSH (n = 94) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** various **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** live birth; OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; cancellation; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** live birth; OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; cancellation; oocyte number; number of embryos cryopreser ed
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT01191710 **Registration date:** 31 August 2010 **Conflict of interest declaration:** none declared **Funding:** none sought **Author correspondence:** yes - drvagpapanikolaou@yahoo.gr (16 September 2021) **Calculations used to obtain absolute ev t numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Suppo t for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list".
Allocation concealment (selection bias)	Low risk	Consulting nurse who had no intervention in the patients' treatment".
Blinding of participants and personnel (performance bias) All outcomes	Low ri k	Authors contacted, stated that doctors were unaware of the protocol, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Uncle r risk	Unstated, subjective outcomes reported.
Incomplete out ome d ta (attrition bias) All outcomes	Low risk	ITT analysis performed. One cycle cancelled in the GnRH antagonist group and three in the GnRH agonist group. Attrition per arm <10%.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms.

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Parsanezhad 2017

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** multicentre **Recruitment period:** January 2014 to May 2014 **Sample size (total randomised):** 160
Participants	**Inclusion criteria:** age 20-38 years; BMI 19-29 kg/m^2; regula menstrual cycles (25-35 days); no relevant systemic disease, severe endometriosis or uterine or ian ab ormalities; ≤3 previous ART cycles; no previous low response **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 40) **Arm 2:** long agonist lus FSH (n = 40) **Arm 3:** long agon st pl s rFSH (n = 40) **Arm 4:** lo g agonist plus rFSH & uFSH (n = 40) **Fertil sation method:** IVF or ICSI **Embryo ag at the time of transfer:** cleavage stage (days 2-4) **Lu eal phase support:** intramuscular and vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** IRCT201408116541N7 **Registration date:** 16 September 2014 **Conflict of interest declaration:** none declared **Funding:** "Supported by Shiraz University of Medical Sciences (grant number 7249)." **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no

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Parsanezhad 2017 *(Continued)*

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"person independent of the research team using a computer-generated random-number list".
Allocation concealment (selection bias)	Low risk	"person independent of the research te m using a omputer-generated random-number list".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blinded" trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blinded" trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed N loss to follow-up.
Selective reporting (reporting bias)	High risk	Study retros ectively registered.
Other bias	High risk	Trial conducted post-2010 and retrospectively registered. Multicentre study. Effe t si difference lower than two-fold between trial arms.

Perino 2002

Study characteristics

Methods	**Design:** randomised controlled trial **Co ntry:** Italy **Lang age:** English **Sett ng:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 94
Participants	**Inclusion criteria:** women undergoing COS for ICSI **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated

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Perino 2002 *(Continued)*

	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 47)
	Arm 2: long agonist plus rFSH (n = 47)
	Fertilisation method: unstated
	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** oocyte number; number of cleavage-stage embryos; clinical pregnancy; OHSS (moderate to severe)
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** conference abstract
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none unde take
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: no insufficient data in the abstract; author contact details not found)
	Additional comments: -

Risk of bias

Bias	Authors jud emen	Support for judgement
Random sequence generation (selection bias)	Unclea risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unc ar risk	Unstated, subjective outcomes reported (e.g., OHSS).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., OHSS).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed. Attrition unstated.

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Perino 2002 *(Continued)*

Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	Single centre study conducted pre-2010. Timeline unstated therefore not possible to assess recruitment rates.

Pezzuto 2010

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** March 2004 to October 2007 **Sample size (total randomised):** 80
Participants	**Inclusion criteria:** age 20-39 years; healthy f mal s; regular menstrual cycles (26-34 days); BMI 20-25 kg/m^2; FSH <10 IU/l; baseline oestradiol ≤45 pg/ml; normal uterine cavity as diagnosed by hysteroscopy; serum LH <0.5 IU/l on cycle day 6 of timulation **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BM):** yes (<30 kg/m^2) **Subgr up (et nicity):** no
Interventions	**Arm 1:** lo agonist plus rFSH (n = 40) **Arm 2:** long agonist plus rFSH & rLH (n = 40) **Fer ilisation method:** ICSI **Em ryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared

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Pezzuto 2010 *(Continued)*

Funding: unstated

Author correspondence: yes - antoniocosimopezzuto@virgilio.it (23 February 2022)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated randomization list
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only obje tive outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, howe er only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT ana ysis performed. Attrition unstated.
Selective reporting (reporting bias)	Low risk	S lective reporting not detected.
Other bias	Low risk	Single centre study conducted pre-2010. Plausible recruitment rates.

Pilehvari 2016

Study characteristics

Methods	**D sign:** andomised controlled trial **Cou try:** Iran **Language:** English **Setting:** single centre **Recruitment period:** March 2014 to June 2015 **Sample size (total randomised):** 77
Participants	**Inclusion criteria:** at least two of the following three criteria advanced maternal age (≥40); previous low ovarian response (presence of <3 oocytes when using a conventional stimulation protocol); and an abnormal ovarian reserve test (AFC <5-7 follicles or AMH <0.5-1.1 ng/ml)

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Pilehvari 2016 *(Continued)*

	Exclusion criteria: use of any infertility medicine within three months of enrolment; presence of any medical history
	Predicted response as stated by the trialists: predicted low response
	Oocyte donors: no
	Cause of infertility: low ovarian reserve
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus clomifene citrate & hMG (n = 42)
	Arm 2: short antagonist plus rFSH & hMG (n = 35)
	Fertilisation method: unstated
	Embryo age at the time of transfer: cleavage st ge (days 2-4
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number
	Outcomes included in the meta-analysis: one
Notes	**Type of publication:** published full ex manuscript
	Trial registration: IRCT20150119203 1N2
	Registration date: 5 Februa y 201
	Conflict of interest declaration unstated
	Funding: unstated
	Author correspond nce: yes - eshtehrani@yahoo.com (16 September 2021)
	Calculations use to obtain absolute event numbers: no
	Inclu on in meta-analysis: no (unclear risk of selection bias, high risk of other biases; primary review outcomes not reported)
	Additional co ments: -

Risk of bias

Bias	Aut ors' judgement	Support for judgement
Random sequenc genera-tion (selection b as)	nclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (perfor-mance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.

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Pilehvari 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Twelve women cancelled in the clomifene group versus eleven cancelled in the non-clomifene group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	High risk	Trial conducted post-2010. Retrospectively registered.
Other bias	High risk	Trial conducted post-2010 and retrospective y registered. Single centre study with plausible recruitment rates. Effect si difference lower than two-fold between trial arms.

Pournaropoulos 2004

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Greece **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomis d):** 40
Participants	**Inclusion criteria:** age <37 years; non-poor responders **Exclusion criteria:** nstated **Predicted respo se as stated by the trialists:** unstated **Oocyte dono s:** no **Cause f in ertility:** unstated **Subgroup (ag :** no **S bgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 10) **Arm 2:** long agonist plus rFSH & hMG (n = 10) **Arm 3:** long agonist plus rFSH & rLH (n = 20) - two arms merged (see additional comments) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** ongoing pregnancy; oocyte number

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Pournaropoulos 2004 *(Continued)*

	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not fo nd) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection and othe biases; primary review outcomes not reported) **Additional comments:** A total of 40 women undergoing a ng downregulation protocol with GnRH agonist were randomised to one of four groups: 1 rFSH only = 10); 2) rFSH and hMG (n = 10); 3) rFSH and rLH (n = 10); and 4) rFSH and different dose o rLH (n = 10 For the purposes of meta-analysis, we planned to amalgamate groups 3 and 4.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated numbers".
Allocation concealment (selection bias)	Unclear risk	Unstat d
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unst ted however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Unstated.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Prapas 2005

Study characteristics

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Prapas 2005 *(Continued)*

Methods	**Design:** randomised controlled trial
	Country: International (Belgium and Greece)
	Language: English
	Setting: single centre
	Recruitment period: January 2003 to December 2003
	Sample size (total randomised): 148
Participants	**Inclusion criteria:** oocyte donor; age ≤32 years; BMI <30 kg/m^2; reg lar me strual cycles (25-35 days); two normal ovaries based on transvaginal ultrasound findings; no PCO; no endometriosis; no gynaecological or medical disorders; normal karyotype; negative infection scr ening
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: yes
	Cause of infertility: N/A
	Subgroup (age): yes (<35 years)
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH n = 73)
	Arm 2: long agonist plus rFSH (n 75)
	Fertilisation method: N/A
	Embryo age at the tim of transfer: N/A
	Luteal phase support: N/A
Outcomes	**Outcomes repor ed:** OHSS; oocyte number
	Outcomes in uded in the meta-analysis: OHSS
Notes	**Type of pu lication:** published full-text manuscript
	Trial registration: unstated
	Regi tration date: -
	Con ict of interest declaration: unstated
	F nding: unstated
	Author correspondence: yes - iakentro@otenet.gr (16 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -
Risk of bias	

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Prapas 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computerized random number table".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Single blind study", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Single blind study", subjective outcomes rep rted.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT not strictly performe but possib e to obtain absolute numbers from data presented. Two women cancelled n group 1 and four women cancelled in group 2. Attrition <10% in oth trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre 2010. Single centre study with plausible recruitment rates. No concerns regard validity of results. Effect size difference lower than two-fold between tr al arms. No other biases detected.

Prapas 2013

Study characteristics	
Methods	**Design:** randomised c ntrol ed trial **Country:** Greece **Lang age:** English **Setting:** s gle centre **Re ruitment period:** January 2007 to December 2011 **Sample size (total randomised):** 330
Participants	**Inclusion criteria:** low-responding women **Exclusion criteria:** known severe endometriosis (stage III and IV according to the revised American Fertility Society criteria); FSH ≥ 14 mIU/ml **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no

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Prapas 2013 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 162) **Arm 2:** short antagonist plus rFSH (n = 168) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** micronised vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - petustam@m il g (25 February 2022) **Calculations used to obtain absolute ev nt numbers:** no **Inclusion in meta-analysis:** no (u clea risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	**Authors' judgemen**	**upport for judgement**
Random sequence generation (selection bias)	Unclear risk	Random patient choice", exact methodology unstated.
Allocation concealment (selection bias)	Uncl r risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients blinded. Personnel not blinded. Only objective outcomes reported.
Blinding of outcome assessment (detec ion bias) All outcomes	Low risk	Unclear, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Twenty-five women cancelled in the GnRH agonist group, and 38 in the GnRH antagonist group. Attrition >10% in both groups.
Selective reporting (reporting bias)	Unclear risk	Registration unstated.

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Prapas 2013 *(Continued)*

Other bias	Unclear risk	Registration unstated.

Qiao 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** multicentre **Recruitment period:** July 2007 to December 2008 **Sample size (total randomised):** 233
Participants	**Inclusion criteria:** age 18-35 years; BMI 18-29 kg/m norma menstrual cycles **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted normal response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 113) **Arm 2:** long agonist plus FSH (n = 120) **Fertilis tion method:** IVF or ICSI **Embryo age at the time of transfer:** unstated **Luteal phase upport:** intramuscular progesterone
Outcomes	**O tcomes reported:** OHSS; clinical pregnancy; ongoing pregnancy; multiple pregnancy; oocyte number; n mber of embryos cryopreserved **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT00725491 **Registration date:** 30 July 2008 **Conflict of interest declaration:** "JIO, HW, EH and BM are employees of Merck, Sharp and Dohme & Co." **Funding:** "Funded by Merck, Sharp and Dohme & Co. (Whitehouse Station, NJ, USA)." **Author correspondence:** yes - b.mannaerts@merck.com (16 September 2021)

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Qiao 2012 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open-label study", subjective ou comes (OHSS) reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label study", subjective outcomes (OHSS) reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis perform Two cycles cancelled in the antagonist group, and four in the ago ist g oup. Attrition rate <10% in each trial arm.
Selective reporting (reporting bias)	Low risk	Tria conducted pre-2010. Retrospectively registered. Selective reporting not detec ed.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Rabati 2012

Study characteristics

Methods	**D sign:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** January 2011 to February 2012 **Sample size (total randomised):** 136
Participants	**Inclusion criteria:** age ≤35 years; first ART cycle; serum FSH ≤10 IU/l **Exclusion criteria:** previous IVF or ICSI; hyperprolactinaemia; thyroid dysfunction; uterine abnormality; severe endometriosis; secondary infertility **Predicted response as stated by the trialists:** unselected population

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Rabati 2012 *(Continued)*

	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 67)
	Arm 2: short antagonist plus rFSH (n = 69)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** OHSS (moderate to severe) clinical pre nancy; ongoing pregnancy; oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manus ript
	Trial registration: IRCT201205309910N1
	Registration date: 24 June 2012
	Conflict of interest declaration: one dec ared
	Funding: "Isfahan University of Medical Sciences."
	Author correspondence: yes - behkhan@yahoo.com (23 February 2022)
	Calculations used to obt in absolute event numbers: no
	Inclusion in meta-a a ysis: no (unclear risk of selection bias, high risk of other biases; primary review outcomes not reported)
	Additional commen : -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Uncl ar risk	"simple randomization", exact methodology unstated.
Allocation concealment (selection bias)	Unc ear risk	Unstated.
Blinding of participan and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., OHSS).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported (e.g., OHSS).

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Rabati 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis performed. Attrition unstated.
Selective reporting (reporting bias)	High risk	Trial conducted post-2010, retrospectively registered.
Other bias	High risk	Study conducted post-2010, retrospectively registered (IRCT201205309910N1). Single centre trial with plausible recruitment rate.

Raga 1999

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** January to June 199 **Sample size (total randomised):** 30
Participants	**Inclusion criteria:** age ≤35 years o d; previ us low response to uFSH (i.e., <4 follicles with diameter ≥16 mm after 12 days of standard ovaria stimulation) in two previous cycles despite normal oestradiol and FSH levels; normal ovulatory ycles; good physical and mental health **Exclusion criteria:** unstated **Predicted response s s ted by the trialists:** predicted low response **Oocyte donors:** no **Cause of inferti y:** various **Subgr up (age):** no **Subgroup BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** rFSH & hMG without pituitary suppression (n = 15) **Arm 2**: hMG & uFSH without pituitary suppression (n = 15) **F rtilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** micronised vaginal progesterone
Outcomes	**Outcomes reported:** cancellation; oocyte number **Outcomes included in the meta-analysis:** cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated

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Raga 1999 *(Continued)*

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomized list".
Allocation concealment (selection bias)	Low risk	"independently performe "
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open tria subject ve outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	TT ana ysis performed. Two cycles were cancelled in the rFSH group, and six in the uFSH group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	ial conducted pre-2010. Selective reporting not detected.
Other bias	Low sk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Ragni 2012

Study characteris cs

Methods

Design: randomised controlled trial

Country: Italy

Language: English

Setting: multicentre

Recruitment period: September 2008 to August 2010

Sample size (total randomised): 304

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Ragni 2012 *(Continued)*

Participants	**Inclusion criteria:** age 18–42 years; day 3 serum FSH >12 IU/ml on at least two occasions or low response (≤ 3 oocytes with a conventional stimulation protocol) in a previous IVF cycle **Exclusion criteria:** number of previous IVF cycles ≥ 3; cycles requiring the use of spermatozoa from MESA-TESE procedures **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** clomifene citrate without pituitary suppress on (n 148) **Arm 2:** agonist flare plus rFSH (n = 156) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavag stage (days 2-4) **Luteal phase support:** micronised proges e one ablets
Outcomes	**Outcomes reported:** live birth; clinical preg a cy; multiple pregnancy; cancellation; oocyte number **Outcomes included in the meta- nalysis** live birth
Notes	**Type of publication:** published f ll-text manuscript **Trial registration:** NCT01389713 **Registration date:** 8 J ly 2011 **Conflict of interest de lara ion:** none declared **Funding:** "The w rk was supported by Regione Lombardia (Decreto Direttore Generale Sanità 7255/20 8). **Auth r corr spondence:** yes - alessio.paffoni@alice.it (16 September 2021) **Calculations used to obtain absolute event numbers:** no **In lusion in meta-analysis:** yes (sensitivity analysis - high risk of other bias due to early termination) **Additi nal comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated list".
Allocation concealment (selection bias)	Low risk	"Sealed opaque envelopes", SNOSE as confirmed by Alessio Paffoni on 17 September 2021.

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Ragni 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute numbers. Attrition rate >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Conducted up to 2010. Retrospectively registered.
Other bias	High risk	Conducted up to 2010. Ret spe tively r gistered. Multicentre study. No concerns regarding validity of results. E fect size difference lower than two-fold between trial arms. Tria ended prematurely, therefore high risk.

Ramirez 2006

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Spain **Language:** Spanish **Setting:** single centre **Recruitment perio :** Ja ua y to June 2006 **Sample size (to al randomised):** 34
Participants	**Inclusi n crit ria:** ag ≤ 37 years; infertility requiring ART; predicted low response; BMI ≤30 kg/m^2 **Exclus n c iteria:** HIV, HBV and HCV infection; prolactin >25 ng/mL; systemic diseases; >3 previous cycles of ART **Pr dicted response as stated by the trialists:** predicted low response **Oocy e donors:** no **Cau e of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 18) **Arm 2:** short antagonist plus rFSH & rLH (n = 16) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4)

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Ramirez 2006 *(Continued)*

	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** clinical pregnancy; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT01112358 **Registration date:** 28 April 2010 **Conflict of interest declaration:** unstated **Funding:** "Supported by Serono." **Author correspondence:** yes - romeu_alb@gva.es (16 September 2021) **Calculations used to obtain absolute event numbe** no **Inclusion in meta-analysis:** yes (primary analys - low risk o selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgeme t
Random sequence generation (selection bias)	Low risk	Random numbers.
Allocation concealment (selection bias)	Low risk	SNOSE follow d.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Uns ted subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear r	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Six women cancelled in the rFSH group, and four in the rFSH/rLH group. Attrition >10% in both groups.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Rashidi 2005

Study characteristics

Methods	**Design:** randomised controlled trial

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Rashidi 2005 *(Continued)*

	Country: Iran
	Language: English
	Setting: single centre
	Recruitment period: September 2002 to August 2003
	Sample size (total randomised): 60
Participants	**Inclusion criteria:** age ≤35 years; day 2 serum FSH concentration ≤8 IU/l; regular ovulatory cycles; long protocol of pituitary down-regulation
	Exclusion criteria: smoking; previous ovarian cystectomy or o phorec my short GnRH antagonist protocol
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 30)
	Arm 2: long agonist plus rFSH (n = 30)
	Fertilisation method: ICSI
	Embryo age at the time of tr nsfer: cleavage stage (days 2-4)
	Luteal phase support: intram scular progesterone
Outcomes	**Outcomes reporte :** live bir h; multiple pregnancy; oocyte number; number of embryos cryopreserved
	Outcome i clud d in the meta-analysis: live birth
Notes	**Type f publ cation:** published full-text manuscript
	Trial regist tion: unstated
	Registration date: -
	Confli t of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - fatemeh_sarvi@yahoo.com, valrec2@yahoo.com (16 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -
Risk of bias	

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Rashidi 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated list of random numbers".
Allocation concealment (selection bias)	Unclear risk	"sealed envelopes", although unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unclear, although only objective outcomes reported and meta-analysed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Embryologists blinded. Only objective outcom s reported and meta-analysed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. o loss to fo low-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre 2010. Single centre study with plausible recruitment rates. No concerns regard validity of results. Effect size difference lower than two-fold between tr al arms. No other biases detected.

Ravhon 2000

Study characteristics	
Methods	**Design:** randomised c ntrol ed trial **Country:** United Kingdom **Lang age:** English **Setting:** s gle centre **Re ruitment period:** unstated **Sample size (total randomised):** 186
Participants	**Inclusion criteria:** women undergoing COS for ART **Exclusion criteria:** previous low response; previous cycle without fertilisation **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no

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Ravhon 2000 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 125) - two arms merged (see additional comments) **Arm 2:** agonist flare plus rFSH (n = 61) **Fertilisation method:** unstated **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** intramuscular and vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - aravhon@ ezeqin net (25 February 2022) **Calculations used to obtain absolute ev nt numbers:** yes **Inclusion in meta-analysis:** no (u clea risk of selection bias; primary review outcomes not reported) **Additional comments:** All pat nts u ed buserelin acetate and rFSH. Patients began the long protocol on day 2 (group 1, n = 70) or day 21 (group 2, n = 55) of the cycle. Patients in group 3 (n = 61) began the short protocol on day 2 of he cycle. For the purposes of meta-analysis, we planned to amalgamate groups 1 and 2 under a lo g ago ist protocol.

Risk of bias

Bias	Authors' judgement	upport for judgement
Random sequence generation (selection bias)	Unclea risk	"drawing sealed envelopes".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low r sk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection b s) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Absolute numbers extracted from percentages. Thirty-six women lost to follow-up (unaccounted for), and only 150 women started treatment. Additionally, ten women were cancelled in groups 1 & 2; and seven women were cancelled in group 3. Attrition >10%.

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Ravhon 2000 *(Continued)*

Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Study timeline unstated.

Razi 2014

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** March 2013 to August 2013 **Sample size (total randomised):** 40
Participants	**Inclusion criteria:** age <35 years; BMI <30 kg/m ; day 3 FSH serum levels <10 U/l; male infertility or unexplained infertility **Exclusion criteria:** uterine fibroids; mild e dometriosis; hydrosalpinx; history of previous IVF (successful or unsuccessful); history of endocrin disease such as diabetes or thyroid disorders; previous hysteroscopic surgery due to intraute ine esions such as uterine submucosal fibroids or intrauterine adhesions; azoospermia **Predicted response as stated by th trialists:** predicted normal response **Oocyte donors:** no **Cause of infertility** various **Subgroup (age):** yes (35 y ars) **Subgroup (BMI):** y s (<30 kg/m^2) **Subg oup (e hnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 20) **Arm 2:** long agonist plus rFSH & rLH (n = 20) **rtilis tion method:** IVF or ICSI **Emb yo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** IRCT201304302575N4 **Registration date:** 7 October 2013

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Razi 2014 *(Continued)*

Conflict of interest declaration: none declared

Funding: unstated

Author correspondence: yes - fereshtehmohseni73@gmail.com (15 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias, high risk of other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random numbers table."
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however o ly objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated how ver only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT an lysis performed. No loss to follow-up.
Selective reporting (reporting bias)	High risk	Tria conducted post-2010. Retrospectively registered.
Other bias	High ri k	Trial conducted post-2010. Retrospective registration. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Recombinant Human FSH S udy Group 1995

Study characteristi s

Methods

Design: randomised controlled trial

Country: International (European countries)

Language: English

Setting: multicentre

Recruitment period: unstated

Sample size (total randomised): 127

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Recombinant Human FSH Study Group 1995 *(Continued)*

Participants	**Inclusion criteria:** age 18-38 years; regular, ovulatory menstrual cycles (21-35 days); early follicular phase (day 2 to 4) serum levels of the following hormones assayed in a centralised laboratory within a defined range (i.e., FSH <12 mIU/ml, LH <13.5 mIU/ml); TSH within normal range; presence of both ovaries; baseline vaginal US scan <10 follicles in each ovary's largest section; no clinically significant abnormal findings form the haematology, clinical chemistry or urinalysis evaluations; failure to conceive after one or more years of unprotected intercourse **Exclusion criteria:** systemic disease; extrauterine pregnancy in the past 3 months; previous history of severe OHSS; previous IVF failure due to fertilisation failure or a low response to COS **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 60) **Arm 2:** long agonist plus uFSH (n = 63) **Fertilisation method:** IVF **Embryo age at the time of transfer:** unstate **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** live birth; O SS; clinical pregnancy; oocyte number; number of cleavage-stage embryos **Outcomes included in the met analysis:** live birth; OHSS; clinical pregnancy; oocyte number; number of cleavage-stage em yos
Notes	**Type of publicat on:** published full-text manuscript **Trial reg t tion:** nstated **Regi ration date:** - **Conflict of terest declaration:** unstated **Fu ding:** unstated **Auth r correspondence:** none undertaken (author contact details not found) **Calc lations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence.

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Recombinant Human FSH Study Group 1995 *(Continued)*

Allocation concealment (selection bias)	Low risk	SNOSE as confirmed by Van Wely 2011.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes (OHSS) reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes (OHSS) reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but po sible to ob ain absolute event rates. Of 123 patients receiving the interventions, 5 ere ca celled in the rFSH group and four in the uFSH group. Attrition <10% in each of the trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published p 2010 Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicent e study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Revelli 2014

Study characteristics	
Methods	**Design:** randomised controll d trial **Country:** Italy **Language:** English **Setting:** single centr **Recruitm t peri d:** over four years **Samp e size otal randomised):** 695
Participants	**Inclusion cr teria:** predicted low response according to the following criteria: serum day 3 FSH between 10 and 20 IU/L in the presence of estradiol serum level <80 pg/ml; circulating AMH between 0.14 and 1.0 ng/ml; AFC 4-10 **Exclus n criteria:** age >43 years; basal FSH >20 IU/l; undetectable AMH levels; AFC<3 **Pred cted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus clomifene citrate & hMG / rFSH & rLH (n = 355)

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Revelli 2014 *(Continued)*

	Arm 2: long agonist plus hMG / rFSH & rLH (n = 340) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; ongoing pregnancy; miscarriage; cancellation; oocyte number **Outcomes included in the meta-analysis:** clinical pregnancy; ongoing pregnancy; miscarriage; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - aerre99@yahoo.com (16 September 2021) **Calculations used to obtain absolute event numbers:** yes **Inclusion in meta-analysis:** yes (primary analysis low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support fo judgement
Random sequence generation (selection bias)	Low risk	"compu rized algorithm".
Allocation concealment (selection bias)	Low risk	"sequentially-numbered dark envelopes".
Blinding of participants and personnel (performance bias) All outcomes	High r k	No blinding after allocation, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	H h risk	No blinding after allocation, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	CPR and MR expressed in percentages, therefore potential for errors in calculations. Loss to follow-up due to cancelled cycles: 46 in the mild protocol group; and 9 in the long protocol group. Attrition >10% in one of the trial arms.
Selective reporting (reporting bias)	Unclear risk	Trial conducted pre- and post-2010. No mention of trial registration.
Other bias	Low risk	Trial conducted pre- and post-2010, no mention of trial registration. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Rinaldi 2014

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** multicentre **Recruitment period:** January 2008 to December 2012 **Sample size (total randomised):** 349
Participants	**Inclusion criteria:** age 27-38 years; BMI 20-26 kg/m^2;previo s cancelled cycle due to risk of ovarian hyperstimulation; normal hormonal profile; regular ov l ry menstrual cycles; normal uterine cavity **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** pred cted h gh response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 148) **Arm 2:** long agonist plus rFSH (n 201) **Fertilisation meth d:** IVF o ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal hase uppor** intramuscular progesterone
Outcomes	**Outcom s eported:** live birth; OHSS; clinical pregnancy; miscarriage; oocyte number; number of cleavage-sta e embryos **O tcomes included in the meta-analysis:** live birth; OHSS
Notes	**ype of publication:** published full-text manuscript **Tria registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - leo.rinaldi@tiscali.it (23 February 2022) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

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Rinaldi 2014 *(Continued)*

Additional comments: -

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated random assignment schedule for each patient".
Allocation concealment (selection bias)	Low risk	"Sealed and numbered envelopes were used to conceal the treatment allocation until randomization".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"open study", however only objective ou comes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"open study", however o ly objecti e outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly reported but possible to extract absolute event rates. Attrition >10% in the agonist group.
Selective reporting (reporting bias)	Low risk	Selective reporti g not detected.
Other bias	Unclear risk	Multicentr rial conducted pre- and post-2010. Registration status unstated. Unexpla ned uneven number of patients in each group following randomisation.

Ruvolo 2007

Study characteristics	
Methods	**Design:** rand mised controlled trial **Country:** I ly **La guage:** English **Setti g:** single centre **Rec itment period:** September 2004 to February 2005 **mple size (total randomised):** 42
Participants	**Inclusion criteria:** normal basal FSH; BMI <28 kg/m^2; previous low response **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian response **Subgroup (age):** no

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Ruvolo 2007 *(Continued)*

	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 18)
	Arm 2: long agonist plus rFSH & rLH (n = 24)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** oocyte number
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none undertake
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: no (uncl isk of selection bias [allocation concealment unstated]; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	upport for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was realized in blocks of three, using computer-generated random number tables".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low isk	Unstated, however only objective outcomes reported.
Blinding of outco e assessment (detection b as) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.

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Ruvolo 2007 *(Continued)*

Other bias	Low risk	Single centre study conducted pre-2010. Plausible recruitment rates.

Sabouni 2015

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 26
Participants	**Inclusion criteria:** unstated **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** nstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist lus hMG (n = 13) **Arm 2:** short ant gonis lus hMG & uFSH (n = 13) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** blastocyst (day 5+) **Luteal phas support:** unstated
Outcomes	**Outcomes reported:** clinical pregnancy; number of blastocysts **O tcomes included in the meta-analysis:** none
Notes	**Typ of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** "Ferring Pharmaceuticals supplied the following medications: Menopur, Bravelle and Endometrin." **Author correspondence:** none undertaken (author contact details not found) **Calculations used to obtain absolute event numbers:** no

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Sabouni 2015 *(Continued)*

Inclusion in meta-analysis: no (unclear risk of selection and other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, however only objective o tcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, however only obj ctive utcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed N loss to follow-up.
Selective reporting (reporting bias)	Low risk	No details of study registration. Selective reporting not detected.
Other bias	Unclear risk	No det ils of study registration. Single centre study with unclear recruitment timeline

San Roman 1992

Study characteristics

Methods	**Design:** randomised controlled trial **Co ntry:** United States of America **Lang age:** English **Sett ng:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 55
Participants	**Inclusion criteria:** women undergoing COS for ART **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unselected population **Oocyte donors:** no **Cause of infertility:** various

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San Roman 1992 *(Continued)*

	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 26)
	Arm 2: agonist flare plus hMG (n = 29)
	Fertilisation method: IVF
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; miscarriage; oo yte number
	Outcomes included in the meta-analysis: live birth
Notes	**Type of publication:** published full-text manusc pt
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none undertaken (author contact details not found)
	Calculations used to obtain absolu event numbers: no
	Inclusion in meta-analysis: y s (sens tivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors jud emen	Support for judgement
Random sequence generation (selection bias)	Unclea risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. A total of 5 women were cancelled for poor response (two in group 1; and three in group 2). Attrition rate >10% in group 2.

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San Roman 1992 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Sauer 2004

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 74
Participants	**Inclusion criteria:** age 18-39 years; ICSI treatment; BMI <35 kg/m^2; regular menstrual cycles; both ovaries present; no clinical signs of pelvic or ut rine abnormalities; normal cervical cytology; wash-out period completed for any previous VF d ug protocols; serum FSH within normal range **Exclusion criteria:** clinically signifi nt sy temic disease; HIV, hepatitis B or C infection; endometriosis; previously low response; previous ≥3 failed treatments; previous ectopic pregnancy; abnormal gynaecological bleeding **Predicted response as stated b the trialists:** unstated **Oocyte donors:** no **Cause of infertil ty:** v ious **Subgroup (age):** no **Subg oup (BMI):** no **Subgroup (e hnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 25) **A m 2:** short antagonist plus rFSH (n = 24) **Arm 3:** short antagonist plus rFSH & rLH (n = 25) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** various **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** number of cleavage-stage embryos **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript

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Sauer 2004 *(Continued)*

Trial registration: unstated

Registration date: -

Conflict of interest declaration: "WS and GNF are both members of the Ambassadors' Council, Serono, Inc."

Funding: "This study was supported by Serono, Inc., Rockland, MA, USA."

Author correspondence: yes - mvs9@columbia.edu (23 February 2022)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias [alloc tion concealment unstated]; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated, intern based system".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"open label , h wever only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"open bel", however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Attrition <10% in all trial arms.
Selective reporting (reporting bias)	Low ris	Selective reporting not detected.
Other bias	Low risk	Multicentre trial conducted pre-2010. No other biases identified.

Sbracia 2005

Study characteri tics

Methods

Design: randomised controlled trial

Country: Italy

Language: English

Setting: single centre

Recruitment period: July 1999 to July 2001

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Sbracia 2005 *(Continued)*

	Sample size (total randomised): 220
Participants	**Inclusion criteria:** age 40 to <45 years; first cycle of ART **Exclusion criteria:** FSH >10 IU/l; oestradiol >60 ng/ml **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** yes (≥35 years) **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus uFSH (n = 110) **Arm 2:** long agonist plus uFSH (n = 110) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta- nalysis** none
Notes	**Type of publication:** published full-tex manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest dec ara ion:** unstated **Funding:** unstated **Author corre pondence:** yes - marcandrea@hotmail.com (16 September 2021) **Calcul ions used to obtain absolute event numbers:** no **Inclusion in m ta-analysis:** no (unclear risk of selection bias [allocation concealment unstated]; pri-ma y review outcomes not reported) **Addi onal comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence gen a-tion (selection bias)	Low risk	"computer-generated randomization number sequence".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (perfor-mance bias)	Unclear risk	Unstated, subjective outcomes reported.

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Sbracia 2005 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Four women cancelled in each triam arm (total = 8). Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results Effect size difference lower than two-fold between trial arms. No other biases detected.

Sbracia 2009

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** January 2003 t June 2007 **Sample size (total randomis d)** 570
Participants	**Inclusion criteria:** ulli aro s women aged ≥40 years **Exclusion criter a:** age ≥45 years; PCOS; FSH>10 IU/ml; previous IVF cycle **Predicted response s stated by the trialists:** unstated **Oocyt donors:** no **Cause of infer ility:** various **Subgroup (age):** yes (≥35 years) **S bgro p (BMI):** no **Sub roup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 285) **Arm 2:** long agonist plus rFSH (n = 285) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes reported:** miscarriage; cancellation; oocyte number

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Sbracia 2009 *(Continued)*

	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - marcandrea@hotmail.com (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias [allo ation concealment unstated]; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated r ndomization number sequence".
Allocation concealment (selection bias)	Unclear risk	"allocated ra domly".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Uns ated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low ri k	ITT analysis not strictly performed but possible to extract absolute event numbers. Four women gropped out of the study and four were cancelled in the cetrorelix group (total attrition = 8); two women dropped out and seven were cancelled in the control group (n = 9). Attrition <10%.
Selective reporting (reporting bias)	Low ri k	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	w risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Schats 2000

Study characteristics

Methods	**Design:** randomised controlled trial

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Schats 2000 *(Continued)*

	Country: International (Belgium and The Netherlands) **Language:** English **Setting:** multicentre **Recruitment period:** November 1996 to August 1998 **Sample size (total randomised):** 496
Participants	**Inclusion criteria:** age 18-38 years; BMI 18-28 kg/m^2; regular menstrual cycles (25-35 days); tubal factor or grades I/II endometriosis, poor spermatozoa requiring IVF/ICSI, or unexplained infertility; serum FSH and LH normal; prolactin <20 ng/ml; testosterone <3.5 nmol/l; ≤2 previous ART cycles; presence of both ovaries and normal uterus; no treatment with clomifene citrate or gonadotrophins in the month prior to the study **Exclusion criteria:** abnormal gynaecological bleeding of undetermined origin; previous IVF or ICSI failure due to low response to gonadotrophins; previous ICSI failure due to low fertilisation (<20%); previous history of severe OHSS; clinically significant condition/disease; male partner with azoospermia and clinical signs of infection detected in a semen analysis within the previous 12 months; surgical sperm retrieval **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 247) **Arm 2:** long agonist plus uFSH (n = 249) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** micronised vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; multiple pregnancy; ectopic pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** live birth; clinical pregnancy; multiple pregnancy; ectopic pregnancy; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases)

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Schats 2000 *(Continued)*

Additional comments: -

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization lists were held at the pharmacy and patients were randomized after receipt of the prescription from a participating centre".
Allocation concealment (selection bias)	Low risk	"Randomization lists were held at the pharmacy and patients were randomized after recepit of the prescription from a participating centre".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients were not blinded to the interve tion, subjec ive outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"assessor-blind".
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Twenty-seven cycles cancelled in each group (total = 54). Attrition >10% in oth trial groups.
Selective reporting (reporting bias)	Low risk	Trial conducted d published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial cond ted p e-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases dete ted.

Schimberni 2011

Study characteristics	
Methods	**Design:** rand mised controlled trial **Country:** I ly **La guage:** English **Setti g:** single centre **Rec itment period:** 2008 to 2010 **mple size (total randomised):** 501
Participants	**Inclusion criteria:** age <45 years; at least one previous cycle with low response to COS **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian response **Subgroup (age):** no

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Schimberni 2011 *(Continued)*

	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** natural cycle, no gonadotrophins (n = 248)
	Arm 2: short antagonist plus rFSH (n = 253)
	Fertilisation method: unstated
	Embryo age at the time of transfer: unstated
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** oocyte number; pregnancy rate
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** conference abstract
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: none undertak
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: no (insuffici nt data in the abstract; author contact details not found)
	Additional comments: -

Risk of bias

Bias	**Authors' judgemen**	**Support for judgement**
Random sequence genera-tion (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear isk	Unstated.
Blinding of participants and personnel (perfor-mance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome as sessment (detect on b as) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unstated.
Selective reporting (re-porting bias)	Low risk	Selective reporting not detected.

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Schimberni 2011 *(Continued)*

Other bias	Low risk	Single centre study conducted pre-2010. Plausible recruitment rates. No other biases identified.

Schimberni 2016

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** July 2014 to December 2015 **Sample size (total randomised):** 234
Participants	**Inclusion criteria:** predicted low ovarian response **Exclusion criteria:** BMI >30 kg/m^2; PCOS; stage III-IV endometriosis; inflammatory, autoimmune or metabolic disorders; administration of fer lity m dications (gonadotrophins, clomifene citrate) within the previous two months **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** sh t antagonist plus clomifene citrate & rFSH (n = 78) **Arm** short antagonist plus rFSH (n = 78) **Arm 3:** ago ist flare plus rFSH (n = 78) **Fe tilisation method:** ICSI **Emb yo age at the time of transfer:** cleavage stage (days 2-4) **Lute l phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT02201914 **Registration date:** 28 July 2014 **Conflict of interest declaration:** none declared **Funding:** unstated

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Schimberni 2016 *(Continued)*

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (high risk of other biases; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-assisted randomization"
Allocation concealment (selection bias)	Low risk	Allocation concealment undertaken until fter randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All members of the stud team wer blinded to the randomized group".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All members of the st dy team were blinded to the randomized group".
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT not strictly erformed but possible to extract absolute event numbers. Of the randomis d w men, 7 discontinued the intervention in group A; 7 in group B; and 3 in oup . Attrition rates >10% in two trial arms.
Selective reporting (reporting bias)	Low risk	Selec ive reporting not detected. Prospectively registered.
Other bias	High risk	P ospectively registered. The study was modified from the original protocol regi tered for economic reasons, since instead of recFSH plus recLH (Pergoveri , Merck-Serono, Europe) only recFSH (Gonal-F, Meck-Serono) was administered.

Schmidt 2005

Study characteristics

Methods	**Design:** randomised controlled trial **Cou try:** United States of America **Language:** English **Setting:** single centre **Recruitment period:** November 2000 to May 2003 **Sample size (total randomised):** 48
Participants	**Inclusion criteria:** age 25-43 years; low ovarian response **Exclusion criteria:** unstated

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Schmidt 2005 *(Continued)*

	Predicted response as stated by the trialists: predicted low response
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH & hMG (n = 24)
	Arm 2: agonist flare plus rFSH & hMG (n = 24)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: intramuscular progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; oocyte nu ber
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text m nuscr pt
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: uns ated
	Funding: "Supported by an unrestric ed educational grant from Organon Pharmaceuticals, Inc., West Orange, New Jersey, and in part by Ferring Pharmaceuticals, Inc., Suffern, New York."
	Author correspondence yes - nulsen@nso1.uchc.edu (16 September 2021)
	Calculations used t obtain absolute event numbers: yes
	Inclusion in met analysis: no (unclear risk of selection bias [allocation concealment unstated]; primary re iew o tcome not reported)
	Additi al omments: -

Risk of bias

Bias	Au ors' judgement	Support for judgement
Random sequence genera tion (selection bias)	Low isk	"Computer-generated randomization".
Allocation conce lme t (selection bias)	Unclear risk	"Sealed envelopes" used, although unclear if sequentially numbered.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, although only objective outcomes reported.
Blinding of outcome assessment (detection bias)	Low risk	Unstated, although only objective outcomes reported.

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Schmidt 2005 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	ITT not strictly performed but possible to extract absolute event numbers. A total of 24 women (11 in the antagonist group and 13 in the agonist group) discontinued treatment (reasons not specified). Attrition rate >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study w th plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Selman 2002

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** International (Germany and Italy) **Language:** English **Setting:** multicentre **Recruitment period:** December 1 98 to N vember 2000 **Sample size (total randomise):** 267
Participants	**Inclusion criteria:** age 18-38 ye rs; BMI 18-26 kg/m^2; infertility attributable to tubal factor, male factor, or unexplained infertility; serum vels of FSH, LH, and prolactin in the normal range; regular ovulatory menstrual cycles (25 35 d ys); normal uterine cavity; no treatment with gonadotrophins in the month before study; first IVF treatm nt cycle **Exclusion criter a:** gynaecological abnormalities or disease; previous poor response to gonadotroph s used for IUI; history of severe OHSS; current PCOS; azoospermia in the male partner **Predicted re ponse as stated by the trialists:** unstated **Oocyte do ors:** no **Ca se of infertility:** various **Subgroup (age):** no **Sub roup (BMI):** no **bgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus uFSH (n = 133) **Arm 2:** long agonist plus rFSH (n = 134) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** intramuscular progesterone

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Selman 2002 *(Continued)*

Outcomes	**Outcomes reported:** live birth; clinical pregnancy; multiple pregnancy; miscarriage; oocyte number; number of cleavage-stage embryos; number of embryos cryopreserved **Outcomes included in the meta-analysis:** live birth; clinical pregnancy; multiple pregnancy; miscarriage; oocyte number; number of cleavage-stage embryos; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - selmanha@yahoo.com (16 Septembe 2021) **Calculations used to obtain absolute event numbers:** n **Inclusion in meta-analysis:** yes (primary analys) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstate
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open l bel study", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label study", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute numerators and denominators. Two cycles were cancelled in the uFSH group, and 1 in the rFSH group. Attrition rate per arm <10%.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Selman 2010

Study characteristics

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Selman 2010 *(Continued)*

Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** January 2008 to February 2009 **Sample size (total randomised):** 188
Participants	**Inclusion criteria:** age 27 to 38 years; tubal factor, male factor or idiopathic infertility; normal serum hormonal profile; regular ovulatory menstrual cycles; presence of a normal uterine cavity; BMI of 20-26 kg/m^2; first ART cycle **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & uFSH (n = 63) **Arm 2:** long agonist plus rFSH (n = 65) **Arm 3:** long agonist plus uFSH (n = 60) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** clinical pregnancy; miscarriage; cancellation; oocyte number **Outcomes included in the meta-analysis:** clinical pregnancy; miscarriage; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

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Selman 2010 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random assignment".
Allocation concealment (selection bias)	Low risk	"Sealed and numbered envelopes used to conceal the treatment allocation until randomization".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Open-label" study, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Open-label" study, however only o jective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. A tal of four cycles were cancelled (1 in group A; 2 in group B; and 1 in group C). Attrition rate per arm <10%.
Selective reporting (reporting bias)	Low risk	Trial conducted a d publ shed pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No conce ns ega ing validity of results. Effect size difference lower than two-fold b twee tria arms. No other biases detected.

Serafini 2006

Study characteristics

Methods	**Design:** n omised controlled trial **Coun ry:** Bra il **Language:** nglish **Se ting:** multicentre **Recru tment period:** July 2002 to August 2005 **Sample size (total randomised):** 323
Participants	**Inclusion criteria:** age 21-39 years; BMI <25 kg/m^2 two functional ovaries; anatomically normal uterine cavity (hysterosalpingogram or hysteroscopy); ≤3 previous ART attempts; normal early follicular phase hormone profile; no history of low ovarian response in previous IVF/ICSI cycles; no untreated endocrine disease; no gonadotrophin therapy within the preceding three months; SFA showing ≥1% normal morphology **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no

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Serafini 2006 *(Continued)*

	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH & uhCG (n = 110)
	Arm 2: short antagonist plus rFSH (n = 107)
	Arm 3: long agonist plus rFSH (n = 106)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: intramuscular and vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; c ncellation; oocyte number
	Outcomes included in the meta-analysis: OHSS; c nical p egnancy; cancellation; oocyte number
Notes	**Type of publication:** published full-text man script
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: nstated
	Funding: unstated
	Author correspondence: non undertaken
	Calculations used to obtain ab lute event numbers: no
	Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)
	Additional comments:

Risk of bias

Bias	Authors j dgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization sequence of allocation".
Allocation concealment (selection bias)	Low risk	"research nurse handed each patient a unique identification envelope in sequential, chronological order".
Blinding of participants and personnel (pe fo mance bias) All outcomes	High risk	"open" study, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open" study, subjective outcomes reported.

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Serafini 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. A total of 23 women withdrew consent: 4 in group A; 11 in group B; and 8 in group C. Attrition >10% in group B.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Shamma 2003

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 29
Participants	**Inclusion criteria:** oocyte donors **Exclusion criteria:** unstated **Predicted response as stated b the trialists:** unstated **Oocyte donors:** yes **Cause of inferti ty:** N/ **Subgro p (a e):** no **Subg oup (BMI):** no **Subgroup (e hnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & hMG (n = 17) **A m 2:** short antagonist plus rFSH & hMG (n = 12) **Fert isation method:** N/A **Embryo age at the time of transfer:** N/A **Luteal phase support:** N/A
Outcomes	**Outcomes reported:** clinical pregnancy; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated

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Shamma 2003 *(Continued)*

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: none undertaken (author contact details not found)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated howeve only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	clear
Selective reporting (reporting bias)	Low risk	ial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low sk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated.

Shu 2019

Study characteristics

Methods

Design: randomised controlled trial

Country: China

Language: English

Setting: multicentre

Recruitment period: May 2014 to December 2015

Sample size (total randomised): 610

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Shu 2019 *(Continued)*

Participants	**Inclusion criteria:** age 20–37 years; BMI 18–24 kg/m^2; weight 40–80 kg; regular menstrual cycles (21–35 days); no previous ART; basal FSH <10 U/l and LH <10 U/l; normal uterine anatomy confirmed by transvaginal ultrasound examination and in some cases hysterosalpingography and hysteroscopy; no evidence of hydrosalpinx or ovarian cyst or endometrioma; AFC >6 **Exclusion criteria:** PCOS; endometriosis stage III/IV; hyperprolactinaemia or other significant systemic disease (endocrine or metabolic abnormalities); use of the following drugs within one month prior to randomisation: clomifene citrate, metformin, gonadotropin or GnRH analogues; smoking (>10 cigarettes/day) within 3 months of recruitment; history of chemotherapy, radiotherapy, or ovarian surgery **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & hMG (n = 305) **Arm 2:** long agonist plus rFSH (n = 305) **Fertilisation method:** unstated **Embryo age at the time of transfer:** cleavage tage (days 2-4) **Luteal phase support:** intramusc lar prog sterone
Outcomes	**Outcomes reported:** clinica preg ancy; ongoing pregnancy; multiple pregnancy; cancellation; oocyte number **Outcomes included in the meta analysis:** clinical pregnancy; ongoing pregnancy; multiple pregnancy; cancellation; ooc te n mber
Notes	**Type of publicat on:** publi hed full-text manuscript **Trial re str tion:** hiCTR-TRC-14004552 **Regi ration date:** 21 April 2014 **Conflict of i terest declaration:** none declared **Funding:** "The study was supported by projects from the National 973 program (2012CB944902), Rese rch fund of National Health and Family Planning Commission of China (201402004, 201002013), and the Jia gsu Province Special Program of Medical Science (BL2012009, ZX201110, FXK201221)." **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement

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Shu 2019 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Random blocks."
Allocation concealment (selection bias)	Low risk	"Independent statistician provided sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study, subjective outcomes rep rted.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. One woman cancelled in group B (rFSH) due to low ovarian response. Attrition 10% in both groups.
Selective reporting (reporting bias)	Low risk	Trial prospectively registe d. All outcomes reported as stated in the registration.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Multicentre study. Effect size differenc l wer than two-fold between trial arms. No other biases detected.

Siristatidis 2022

Study characteristics	
Methods	**Design:** randomised c trolled trial **Country:** Greece **Language:** Engl h **Setting:** mult centre **Recruitm nt period:** July 2017 to April 2019 **Sample size (total randomised):** 81
Participants	**Incl sion criteria:** age 35-40 years; regular menstrual cycles (24-35 days); normal endocrine function (n rmal prolactin, TSH, FSH ≤ 15 IU/ml); normal transvaginal ultrasound; first or second IVF/ICSI cycle **Excl sion criteria:** age <35 and > 40 years; endocrine or metabolic disorders (e.g., PCO[S]); uterine pathology; basal FSH >15 IU/ml; previous ovarian surgery; BMI ≥ 35 kg/m^2 **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** yes (≥35 years) **Subgroup (BMI):** no

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Siristatidis 2022 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** agonist flare plus rFSH & uhCG (n = 40) **Arm 2:** agonist flare plus rFSH (n = 41) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; miscarriage; cancellation; ocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** EudraCT Number 2016-005208 24 **Registration date:** 12 July 2012 **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute vent numbers:** no **Inclusion in meta-analysis** yes (s n itivit analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgemen	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done using sealed opaque envelopes marked as “group 1” and “group 2”. The randomization list was prepared centrally for the three participating Units [research centers]. Each patient’s assignment to a treatment group was made by calling the Unit’s midwife who had 2 envelopes with the above indications and who was not present when the couple was informed by two members of the research team."
Allocation concealment (selection bias)	Low isk	"Randomization was done using sealed opaque envelopes marked as “group 1” and “group 2”. The randomization list was prepared centrally for the three participating Units [research centers]. Each patient’s assignment to a treatment group was made by calling the Unit’s midwife who had 2 envelopes with the above indications and who was not present when the couple was informed by two members of the research team."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study.

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Siristatidis 2022 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 8 cycles were cancelled in the rFSH plus uhCG group, and 7 in the rFSH-only group. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial registered prospectively. Selective reporting not detected.
Other bias	High risk	Trial registered prospectively. The study ended prematurely due to the Covid-19 pandemic.

Söderström-Anttila 1996

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Finland **Language:** English **Setting:** single centre **Recruitment period:** January 1994 to May 1995 **Sample size (total randomised):** 41
Participants	**Inclusion criteria:** age <35 years; oo hea th; no history of familial genetic disorders; no hepatitis B, C or HIV infection **Exclusion criteria:** unstated **Predicted response as stated b the trialists:** unstated **Oocyte donors:** yes **Cause of inferti ty:** N/ **Subgro p (a e):** no **Subg oup (BMI):** no **Subgroup (e hnicity):** no
Interventions	**Arm 1:** long agonist plus uFSH (n = 20) **A m 2:** l ng agonist plus hMG (n = 21) **Fert isation method:** N/A **Embryo age at the time of transfer:** N/A **Luteal phase support:** N/A
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated

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Söderström-Anttila 1996 *(Continued)*

Registration date: -

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: none undertaken (author contact details not found)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized in blocks".
Allocation concealment (selection bias)	Unclear risk	"Treatment allocation was provided in sealed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial, subjective outcomes reported (e.g., cancellation).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open tria subject ve outcomes reported (e.g., cancellation).
Incomplete outcome data (attrition bias) All outcomes	Low risk	TT ana ysis performed. Attrition <10% per trial arm.
Selective reporting (reporting bias)	Low risk	elective reporting not detected.
Other bias	Low sk	Single centre trial with plausible recruitment rates. Study conducted pre-2010.

Sohrabvand 2010

Study characteristics

Methods

D ign: randomised controlled trial

Country: Iran

Language: English

Setting: single centre

Recruitment period: June 2006 to June 2007

Sample size (total randomised): 64

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Sohrabvand 2010 *(Continued)*

Participants	**Inclusion criteria:** age 20-35 years; BMI range of 18-30 kg/m^2; no underlying medical illnesses; no contraindications for pregnancy; normal karyotype; tubal or male factor infertility **Exclusion criteria:** tubal or male factor infertility; PCOS; FSH >12 IU/l **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 32) **Arm 2:** long agonist plus rFSH & hMG (n = 32) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; OHSS; clinica pregnancy; clinical pregnancy; oocyte number **Outcomes included in the meta-analy s:** live birth; OHSS
Notes	**Type of publication:** published full ext manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest decl ra ion:** none declared **Funding:** unstat d **Author orr spond nce:** yes - fsohrabvand@yahoo.com (16 September 2021) **Calcu ation used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Ad itional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence ge era-tion (selection bias)	Low risk	"simple random sampling, using a random numbers table".
Allocation concealment (selection bias)	Unclear risk	"randomly allocated".
Blinding of participants and personnel (performance bias)	Low risk	"double-blind".

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Sohrabvand 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind".
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Two women cancelled in each group (total = 4). Attrition rate <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results Effect size difference lower than two-fold between trial arms. No other biases detected.

Sohrabvand 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** Octobe 2008 t December 2009 **Sample size (total randomis d)** 160
Participants	**Inclusion criteria:** age 20-35 years; PCOS (Rotterdam criteria); BMI 18-30 kg/m^2; no underlying medical illnesses; no cont ain cations for pregnancy **Exclusio c teria** BMI>30 kg/m^2; endometriosis; hypo and hypergonadotrophic hypogonadism; hyperpro actina mia; thyroid disorders; ovarian or adrenal neoplasms; Cushing syndrome; infertility due to ca ses other than PCOS; previous history of low ovarian response; male factor infertility **Predicted r ponse as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause f infertility:** PCOS **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 80) **Arm 2:** long agonist plus uFSH (n = 80) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4)

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Sohrabvand 2012 *(Continued)*

	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** live birth; ongoing pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** live birth; ongoing pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript **Trial registration:** IRCT138901193636N1 **Registration date:** 8 April 2010 **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event nu bers:** no **Inclusion in meta-analysis:** yes (primary analysis - w risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgeme t
Random sequence generation (selection bias)	Low risk	"random umbers table".
Allocation concealment (selection bias)	Low risk	"clinic an, ultrasonographer, embryologist and statistician all blinded" to allo-ca n Randomised by clinic secretary.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	cli ician, ultrasonographer, embryologist and statistician all blinded".
Blinding of outcome assessment (detection bias) All outcomes	Low sk	"clinician, ultrasonographer, embryologist and statistician all blinded".
Incomplete outcome data (attrition bias) All outcomes	L w risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Attrition rate <10% in both trial arms. One oocyte collection cancelled in group B due to poor response.
Selective reportin (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

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Strehler 2001

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Italy **Language:** English **Setting:** single centre **Recruitment period:** January 1998 to June 1999 **Sample size (total randomised):** 578
Participants	**Inclusion criteria:** age ≤40 years old; ≤4 previous IVF or ICSI cycles **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** un tated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus hMG (n = 282) **Arm 2:** agonist flare plus rFSH (n 296) **Fertilisation method:** IVF or ICSI **Embryo age at the tim of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes repor ed:** clinical pregnancy; multiple pregnancy; oocyte number **Outcomes in uded in the meta-analysis:** none
Notes	**Type of pu lication:** published full-text manuscript **Tr al registration:** unstated **Regi tration date:** - **Con ict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - erwin.strehler@bnv-gz.de (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selection bias, high risk of other biases; primary review outcomes not reported) **Additional comments:** -
Risk of bias	

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Strehler 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computerized randomization".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed b t possible to extract absolute event numbers. Twenty cycles cancelled in the MG group, and 28 cancelled in the rFSH group. Attrition <10% in b th trial a ms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	High risk	Trial conducted pre 2010. Single centre study with high recruitment rates. Effect size difference l er than two-fold between trial arms. No other biases detected.

Strina 2003

Study characteristics	
Methods	**Design:** randomised c ntrol ed trial **Country:** Italy **Lang age:** English **Setting:** s gle centre **Re ruitment period:** unstated **Sample size (total randomised):** 43
Participants	**Inclusion criteria:** predicted low ovarian response (basal FSH >9 IU/l and/or age >37 years) **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** no

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Strina 2003 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH & rLH (n = 20) **Arm 2:** agonist flare plus rFSH & rLH (n = 23) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertake (uthor contact details not found) **Calculations used to obtain absolute ev nt numbers:** no **Inclusion in meta-analysis:** no (u clea risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	**Authors' judgemen**	**upport for judgement**
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Uncl r risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detec ion bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unstated.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Strina 2003 *(Continued)*

Other bias	Unclear risk	Single centre study. Recruitment rates unclear as study timeline unstated.

Sunde 1994

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Norway **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 146
Participants	**Inclusion criteria:** age <38 years; normoendocrine profile; r gular menstrual cycles; normal SFA **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** nstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus FSH (n = 82) **Arm 2:** long ago ist plu SH (n = 64) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phas support:** unstated
Outcomes	**Outcomes reported:** live birth; oocyte number **O tcomes included in the meta-analysis:** live birth
Notes	**Typ of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** yes

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Sunde 1994 *(Continued)*

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated. however only objective o tcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated. however only obj ctive utcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis not str ctly performed but possible to extract absolute event numbers from percentages. Attrition unstated.
Selective reporting (reporting bias)	Low risk	Trial conduc ed a d published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results ffect size difference lower than two-fold between trial arms. No other biases detected.

Sunkara 2014

Study characteristics

Methods	**Design:** randomised controlled trial **C untry:** United Kingdom **La guage:** English **Sett ng:** multicentre **Recruitment period:** March 2007 to May 2012 **Sample size (total randomised):** 111
Participants	**Inclusion criteria:** previous low response to COS **Exclusion criteria:** age >40 years; single ovary **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no

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Sunkara 2014 *(Continued)*

	Cause of infertility: low ovarian reserve
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH (n = 37)
	Arm 2: agonist flare plus rFSH (n = 37)
	Arm 3: short antagonist plus rFSH (n = 37)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: various
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** ongoing pregnancy; cance ation; oocy number
	Outcomes included in the meta-analysis: ongoing pregna cy; cancellation; oocyte number
Notes	**Type of publication:** published full-text man script
	Trial registration: EUCTR2006-004460-31 B and ISRCTN27044628
	Registration date: 9 January 2009
	Conflict of interest declaration: one declared
	Funding: "This study was fund d by he ssisted Conception Unit, Guy's Hospital, London, United Kingdom."
	Author correspondence: none ndertaken
	Calculations used to obt in absolute event numbers: no
	Inclusion in meta-a a ysis: yes (primary analysis - low risk of selection and other biases)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"third party, distant, Internet-based block randomization".
Allocation concealment (selection bias)	Low isk	"third party, distant, Internet-based block randomization to ensure complete allocation concealment".
Blinding of partic pan s and personnel (perfor mance bias) All outcomes	High risk	Blinding of some personnel but not all. Subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.

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Sunkara 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Attrition >10% in at least one of the trial arms.
Selective reporting (reporting bias)	Low risk	Trial initiated pre-2010 and continued post-2010. Registration undertaken on 9 January 2009. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre- and post-2010. Trial protocol published prospectively in a peer-reviewed journal. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Tan 1991

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United Kingdom **Language:** English **Setting:** unstated **Recruitment period:** unstated **Sample size (total randomised):** 08
Participants	**Inclusion criteria:** first cycle of COS for ART **Exclusion criteria:** unstated **Predicted response s s ted by the trialists:** unstated **Oocyte donors:** no **Cause of inferti y:** unstated **Subgr up (age):** no **Subgroup BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** hMG without pituitary suppression (n = 81) **Arm 2:** clomifene citrate & hMG without pituitary suppression (n = 77) **A m 3:** short agonist flare plus hMG (n = 74) **Arm 4:** long agonist plus hMG (n = 76) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number; embryo number; implantation rate; pregnancy rate; multiple pregnancy; ongoing pregnancy

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Tan 1991 *(Continued)*

	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (insufficient data in the abstract; uthor contact details not found) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, weve only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear isk	Unstated.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	Number of centres unstated. Timeline and recruitment rates unstated.

Tan 1992

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** United Kingdom **Language:** English **Setting:** single centre

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Tan 1992 *(Continued)*

	Recruitment period: 1 year as confirmed by the authors
	Sample size (total randomised): 91
Participants	**Inclusion criteria:** first IVF cycle
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 46)
	Arm 2: agonist flare plus hMG (n = 45)
	Fertilisation method: unstated
	Embryo age at the time of transfer: cleavage st ge (days 2-4)
	Luteal phase support: hCG
Outcomes	**Outcomes reported:** clinical preg ancy; cancellation
	Outcomes included in the meta-an lysis: clinical pregnancy; cancellation
Notes	**Type of publication:** publishe full-text manuscript
	Trial registration: unstated
	Registration date:
	Conflict of interest declaration: unstated
	Funding: uns ated
	Author cor espondence: yes - jlyovich@pivet.com.au (16 September 2021)
	Calculations used to obtain absolute event numbers: no
	In lusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)
	A ditional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random tables". Appropriate randomisation as confirmed by John Yovich via email on 22/09/2021 - "strictly randomised selection process".
Allocation concealment (selection bias)	Low risk	"serially numbered sealed envelopes".

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Tan 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"the RCT was double-blinded from the selection process" as confirmed by John Yovich on 23/09/2021.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"the RCT was double-blinded from the selection process" as confirmed by John Yovich on 23/09/2021.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Four women cancelled in group 1 and six in group 2. Attrition >10% in group 2.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010 Sele tive re orting not detected.
Other bias	Low risk	Trial conducted pre-2010 S ngle entre tudy. Recruitment rates plausible as confirmed by John Yovic . Effect siz difference lower than two-fold between trial arms. No other bias s detected.

Tarlatzis 2006

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** International (Greece Isra l Poland and Turkey) **Language:** English **Setting:** multicentre **Recruitment perio :** un tated **Sample size (to al randomised):** 114
Participants	**Inclusi n cri ria:** ag 18-37 years; normal uterus and two ovaries; scheduled to undergo IVF with ICSI; ovula ory cyc es (24-35 days); maximum FSH 12 IU/l; maximum prolactin <40 mIU/l **Exclusion riteria:** previous low response (<3 oocytes recovered after COS) **Pr dicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cau e of infertility:** various **bgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & rLH (n = 55) **Arm 2:** long agonist plus rFSH (n = 59) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4)

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Tarlatzis 2006 *(Continued)*

	Luteal phase support: micronised vaginal progesterone
Outcomes	**Outcomes reported:** live birth; OHSS; clinical pregnancy; miscarriage; cancellation; oocyte number **Outcomes included in the meta-analysis:** live birth; OHSS; clinical pregnancy; miscarriage; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis low risk o selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgem nt
Random sequence generation (selection bias)	Low risk	"compute program".
Allocation concealment (selection bias)	Low risk	"do ble-bl nd study", "sealed evelopes containing details of the randomized treatment [which] were to be opened only in case of emergency".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	double-blind study".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Two women were cancelled in the placebo group.Attrition rate <10% in both trial arms.
Selective reporting (reporting bias)	Low isk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Taronger 2018

Study characteristics

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Taronger 2018 *(Continued)*

Methods	**Design:** randomised controlled trial **Country:** Spain **Language:** English **Setting:** single centre **Recruitment period:** 2013 to 2017 **Sample size (total randomised):** 234
Participants	**Inclusion criteria:** age <40 years; at risk of poor ovarian response **Exclusion criteria:** anovulation; presence of uterine pathology; unc rrected hydrosalpinx; FSH >20 mIU/ml; non-detectable AMH; AFC <3; severe male factor **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH & hM (n = 117) **Arm 2:** short antagonist plu hMG 117) **Fertilisation method:** ICSI **Embryo age at the time f tran fer:** cleavage stage (days 2-4) **Luteal phase suppo t:** vaginal progesterone
Outcomes	**Outcomes repo ed:** ve b rth; OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; ectopic pregnancy; canc llation; oocyte number; cleavage embryo number **Outcomes in uded in the meta-analysis:** live birth; OHSS; clinical pregnancy; ongoing pregnancy; misca riage ectopic pregnancy; cancellation; oocyte number; cleavage embryo number
Notes	**Type of publi tion:** published full-text manuscript **Tr al registration:** EUCTR2013-002027-42-ES **R gistration date:** 14 August 2013 **Con ict of interest declaration:** none declared **Funding:** "This work was supported by: The Health Research Institute La Fe (IIS La Fe) and Spanish Clinical Research Network, SCReN-IIS La Fe, PT17/0017/0035 (Valencia, Spain). No external funding was used for this study." **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

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Taronger 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"web-based program".
Allocation concealment (selection bias)	Low risk	"perofmred in the clinical trials section of the hospital's pharmacy department", thus centrally managed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open label" study, subjective outcomes reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open label" study, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly pe formed but possible to extract absolute event numbers. Five women excluded in the rFSH/hMG group, and 8 excluded in the hMG group. Four cycles cancelled in the rFSH group and six in the hMG group (total = 23). Attrition >10% in the hMG group.
Selective reporting (reporting bias)	Low risk	Trial conducted pos 2010. Registration undertaken prospectively. All outcomes reported as sta ed in the registration.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausib e recruitment rates. Effect size difference lower than two-fold betwe n trial arms.

Tehraninejad 2009

Study characteristics

Methods	**Design** randomised controlled trial **Country** I n **Language:** English **Se ting:** single centre **Re ruitment period:** from 2005 to 2006 **Sample size (total randomised):** 70
Participants	**Inclusion criteria:** low-responding women **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian response **Subgroup (age):** no

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Tehraninejad 2009 *(Continued)*

	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus hMG (n = 35)
	Arm 2: long agonist plus hMG (n = 35)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** ongoing pregnancy; miscarriage; oocyte num er
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manuscrip
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: none declar d
	Funding: unstated
	Author correspondence: yes - tehraninej d@ oyaninstitute.org (16 September 2021)
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: no (unc ar isk of selection bias [allocation concealment unstated]; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	**Authors' judgement**	**S pport for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated random numbers".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unc ar risk	"Both the embryologist and statistician involved in the study were blinded to the treatment allocation", unclear whether patients blinded.
Blinding of outco e assessment (detection ias) All outcomes	Low risk	"Both the embryologist and statistician involved in the study were blinded to the treatment allocation".
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. One cycle cancelled in the short antagonist group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Tehraninejad 2009 *(Continued)*

Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Tehraninejad 2010

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** April 2006 to March 2007 **Sample size (total randomised):** 95
Participants	**Inclusion criteria:** age <35 years; PCOS (Rotterdam criteria); first ICSI treatment; basal FSH <10 IU/l **Exclusion criteria:** secondary infertility; p evious IVF or ICSI; thyroid dysfunction; hyperprolacti-naemia; uterine abnormalities; solitary ovary **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** yes (<35 years **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus hMG (n = 48) **Arm 2** long agonist plus hMG (n = 47) **Fertilisati n method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Lute l phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; ongoing pregnancy; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - nasiri.roya1@gmail.com (16 September 2021)

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Tehraninejad 2010 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomized schedules".
Allocation concealment (selection bias)	Unclear risk	"schedules (…) were sealed in envelop s and handed to the patients", however unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes re orted
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not stric y performed but possible to extract absolute event numbers. Two women lost to follow-up in the antagonist group and three women did not re eive int rvention in the agonist group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-f ld between trial arms. No other biases detected.

Tehraninejad 2011

Study characteristics

Methods	**Desig :** randomised controlled trial **Cou try:** Iran **Language:** English **Setting:** single centre **Recruitment period:** January 2008 to January 2010 **Sample size (total randomised):** 300
Participants	**Inclusion criteria:** age <38 years; normal basal serum FSH; 20≤ BMI <30kg/m^2; and regular menstrual cycles

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Tehraninejad 2011 *(Continued)*

	Exclusion criteria: PCOS; severe endometriosis; low response in previous treatment cycles and history of repeated IVF failure (>3 previous failed cycles) **Predicted response as stated by the trialists:** predicted normal response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & hMG (n = 150) **Arm 2:** short antagonist plus rFSH & hMG (n = 150) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage st ge (days 2-4 **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full tex manuscript **Trial registration:** IRCT138 0228395 N1 **Registration date:** 19 June 2011 **Conflict of interest decl ration** unstated **Funding:** unstated **Author correspondence:** yes - jafarabadi@tums.ac.ir (15 September 2021) **Calculatio s use to obtain absolute event numbers:** no **Inclu on in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcom s [l ve birth and/or OHSS]) **Additional co ments:** -

Risk of bias

Bias	Aut ors' judgement	Support for judgement
Random sequence generation (selection b as)	Low risk	"sequence of computer generated random numbers (0 or 1)".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.

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Tehraninejad 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial conducted up to 2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted up to 2010. Retrospectively r giste ed. Single centre study with plausible recruitment rates. Effect si differenc lower than two-fold between trial arms.

Tehraninejad 2017

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Iran **Language:** English **Setting:** single centre **Recruitment period:** October 014 t April 2016 **Sample size (total randomis d):** 140
Participants	**Inclusion criteria:** age 20-35 years; male factor, tubal or unexplained infertility; regular menstrual cycles (21-35 days); ormal uterine anatomy and function according to hysterosalpingography, hysteroscopy or transvaginal ult asonography; normal ovaries according to transvaginal ultrasonography in the past 6 mo ths; s rum FSH <8 IU/l; unexplained infertility; normal ovulatory function; normal SFA (WHO) **Exclu on cri eria:** endometriosis; ovulation disorders including PCOS; low response; previous history of >3 u successful IVF cycles; malformations of sexual organs **Predicted res onse as stated by the trialists:** unstated **Oocyte donors:** no **Cause f infertility:** unstated **Sub roup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH & hMG (n = 70) **Arm 2:** long agonist plus rFSH & rLH (n = 70) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4)

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Tehraninejad 2017 *(Continued)*

	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; miscarriage **Outcomes included in the meta-analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** IRCT2016092720351N3 **Registration date:** 31 October 2016 **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbe** no **Inclusion in meta-analysis:** yes (sensitivity analysis - includi g all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgem nt
Random sequence generation (selection bias)	Low risk	"random umbers table".
Allocation concealment (selection bias)	Low risk	"allocated by the clinic secretary".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	clinician, ultrasonographer, embryologist and statistician were not blinded", however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"clinician, ultrasonographer, embryologist and statistician were not blinded", however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	High risk	Trial conducted post-2010. Retrospectively registered.
Other bias	High risk	Trial conducted post-2010 and retrospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Tesarik 2002

Study characteristics

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Tesarik 2002 *(Continued)*

Methods	**Design:** randomised controlled trial
	Country: Spain
	Language: English
	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 253
Participants	**Inclusion criteria:** oocyte donors aged 21-28 years; healthy volunte rs
	Exclusion criteria: unstated
	Predicted response as stated by the trialists: predicted normal response
	Oocyte donors: yes
	Cause of infertility: N/A
	Subgroup (age): yes (<35 years)
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus rFSH & uFSH (n = 127
	Arm 2: long agonist plus rFSH & rLH & uFSH (n = 126)
	Fertilisation method: N/A
	Embryo age at the time of transfer: N/A
	Luteal phase support: N/A
Outcomes	**Outcomes reporte :** o cyte number
	Outcomes incl ed in the meta-analysis: none
Notes	**Type f publi ation:** published full-text manuscript
	Trial reg ration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: unstated
	Author correspondence: yes - cmendoza@ugr.es (16 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement

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Tesarik 2002 *(Continued)*

Random sequence generation (selection bias)	Low risk	"computer-generated randomization list".
Allocation concealment (selection bias)	Unclear risk	"allocated at random".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective out omes port d.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to f low-up.
Selective reporting (reporting bias)	Low risk	Trial conducted and publi hed pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns rega d g validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

The European and Israeli Study Group 2002

Study characteristics	
Methods	**Design:** randomised c trolled trial **Country:** Internatio al (Denmark, Germany, Israel, Switzerland, The Netherlands and United Kingdom) **Language:** Engl h **Setting:** mult centre **Recruitm nt period:** May 1999 to November 2000 **Sample size (total randomised):** 781
Participants	**Incl sion criteria:** age 18-38 years; regular ovulatory menstrual cycles (24-36 days); no evidence of u rine or ovarian anomalies on ultrasound; normal baseline serum parameters for haematology, bloo chemistry and urinalysis in the previous 12 months; baseline endocrine levels within normal limits **Exclusion criteria:** BMI <18 and >29 kg/m^2; systemic disease; endocrine disorder; ovarian cyst; contraindications to gonadotrophins or GnRH agonists; smoking (>10 cigarettes/day); alcohol or drug abuse; currently breastfeeding, pregnant or contraindication to pregnancy; OHSS in previous COS cycle **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no

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The European and Israeli Study Group 2002 *(Continued)*

	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 395)
	Arm 2: long agonist plus rFSH (n = 386)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: unstated
	Luteal phase support: variable
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; ongoing pregnancy; multiple regnancy; miscarriage
	Outcomes included in the meta-analysis: OHSS; clinical pr gnancy ongoing pregnancy; multiple pregnancy; miscarriage
Notes	**Type of publication:** published full-text manuscr pt
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration: unstated
	Funding: Ferring Pharmaceuticals
	Author correspondence: none undertaken
	Calculations used to obtai abso ute event numbers: no
	Inclusion in meta-analysis: yes (p imary analysis - low risk of selection and other biases)
	Additional comments: -

Risk of bias

Bias	**Authors' judgement**	**upport for judgement**
Random sequence generation (selection bias)	Low risk	"Computer-generated" allocation sequence.
Allocation concealment (selection bias)	Low risk	"Batches of sealed envelopes", sequentially numbered.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open-label study", subjective outcomes reported.
Blinding of outco e assessment (detection b as) All outcomes	High risk	"Open-label study", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed, but absolute numerator and denominator values available. Twenty-two women dropped out from the Menotropin group and thirty-two dropped out from the rFSH group before receiving treatment. Attrition in each group <10%.

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The European and Israeli Study Group 2002 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

The European and Middle East Ogalutran Group 2001

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** International (twelve centres in nine countries in E rope and the Middle East) **Language:** English **Setting:** multicentre **Recruitment period:** unstated **Sample size (total randomised):** 337
Participants	**Inclusion criteria:** age 18 to <39 years; BMI 1 29 kg/m^2; regular menstrual cycles; willing to give written informed consent. **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BM):** yes (<30 kg/m^2) **Subgr up (et nicity):** no
Interventions	**Arm 1:** sh t antagonist plus rFSH (n = 226) **Arm 2:** long agonist plus rFSH (n = 111) **Fer ilisation method:** IVF or ICSI **Em ryo age at the time of transfer:** various **Luteal phase support:** variable
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; cancellation; oocyte number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** OHSS; clinical pregnancy; ongoing pregnancy; miscarriage; cancellation; oocyte number; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** -

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The European and Middle East Ogalutran Group 2001 *(Continued)*

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: yes - h.horren@organon.oss.akzonobel.nl (15 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Interactive voice system".
Allocation concealment (selection bias)	Low risk	Centralised allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open-label study", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label study", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysi performed. Eleven cycles were cancelled in the GnRH antagonist group nd 5 in the GnRH agonist group. Attrition <10%.
Selective reporting (reporting bias)	Low risk	Tria conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Thuesen 2012

Study characteristics

Methods

Design: randomised controlled trial

Country: Denmark

Language: English

Setting: single centre

Recruitment period: February 2009 to June 2010

Sample size (total randomised): 62

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Thuesen 2012 *(Continued)*

Participants	**Inclusion criteria:** age 25-37 years; BMI >18 and <30 kg/m^2; regular menstrual cycles (24-35 days); presence of two ovaries; tubal factor, mild endometriosis, mild male factor or unexplained infertility; presumed to be ovulatory; normal uterus; normal baseline endocrine profile **Exclusion criteria:** PCOS; endometriosis stage III/IV; severe male factor require ICSI; previous severe OHSS; >3 previous COS cycles; previous low response during COS: previous unsuccessful fertilisation (≤20% of the retrieved oocytes); recurrent miscarriage; FSH >12 IU/l or LH >12 IU/l; contraindications for the use of gonadotrophins or GnRH analogues; recent history of epilepsy; HIV infection; diabetes or cardiovascular, gastrointestinal, hepatic, renal or pulmonary disease; pregnancy, lactation or contraindication to pregnancy; current or past abuse of alcohol or drugs; abnormal patient karyotype **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus rFSH (n = 16) **Arm 2:** long agonist plus rFSH & uhCG (n = 6) - three arms merged (see additional comments) **Fertilisation method:** IVF **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** micronised vaginal progesterone tablets
Outcomes	**Outcomes reported:** live birth OHSS; clinical pregnancy; miscarriage; ectopic pregnancy; cancellation; oocyte number; cleavage embryo number; number of embryos cryopreserved **Outcomes included in the meta-analysis:** live birth; OHSS; clinical pregnancy; miscarriage; ectopic pregnancy; cancellation; oocyte number; cleavage embryo number; number of embryos cryopreserved
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT00844311 **Registration date:** 16 February 2009 **Conflict of interest declaration:** none declared **Funding:** "Ferring Pharmaceuticals, Research and Development, provided funds for the endocrine measurement." **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments :**A total of 62 women undergoing a long GnRH agonist downregulation protocol were randomly allocated to treatment with rFSH only (one group, n = 16) or treatment with rFSH plus variable dosing of hCG (three groups, n = 46). The three groups receiving hCG were merged for the purposes of meta-analysis.
Risk of bias	

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Thuesen 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomization list was generated by computerized block randomization. Block size was 12 resulting in a balanced allocation in treatment groups for each 12 patients. The blocking was unknown to all individuals involved in allocating treatments and data collection".
Allocation concealment (selection bias)	Low risk	"From the randomizaiton list, a secretary prepared sequentially numbered, opaque sealed envelopes. Independent monitors from the GCP unit at Copenhagen University verified that the envelopes w re sealed. The envelopes were opened in consecutive order by one of the invest gators after verbal and written informed consent".
Blinding of participants and personnel (performance bias) All outcomes	High risk	"After randomization, the study was open wit out bli idng for the investigator and the patients; however, the lab tech icians scoring the embryos were blinded to the treatment protocol Subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"After randomization, th study was pen without blinidng for the investigator and the patients; how ver, the lab technicians scoring the embryos were blinded to the treatment proto ol . Subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to obtain absolute event numbers. Two women ithdr w in the hCG group. Additionally, one woman was cancelled in the hCG group and no women were cancelled in the rFSH-only group. Attrition 0% n both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conduct d p -and up to 2010. Registration undertaken prospectively. All outcomes ported as stated in the registration.
Other bias	Low risk	Trial onduc ed post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Toftager 2016

Study characteristics	
Methods	**Design:** rand mised controlled trial **Country:** Denmark **Langu ge:** English **Sett ng:** multicentre **Recruitment period:** January 2009 to December 2013 **Sample size (total randomised):** 1050
Participants	**Inclusion criteria:** age <40 years **Exclusion criteria:** previous ART cycles; uterine anomalies; SSR; reduced renal or hepatic function **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no

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Toftager 2016 *(Continued)*

	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 534)
	Arm 2: long agonist plus rFSH (n = 516)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: unstated
Outcomes	**Outcomes reported:** live birth; OHSS; ongoing pregn y; mis rriage; cancellation; oocyte number; number of embryos cryopreserved
	Outcomes included in the meta-analysis: live b th; OHSS; ongoing pregnancy; miscarriage; cancellation; oocyte number; number of embryos cryoprese ed
Notes	**Type of publication:** published full-text manuscript
	Trial registration: NCT00756028
	Registration date: 19 September 2008
	Conflict of interest declaration: one dec ared
	Funding: "An unrestricted rese rch gr t was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, U A (MSD)."
	Author correspondence one undertaken
	Calculations used t obt in absolute event numbers: no
	Inclusion in met an lysis yes (primary analysis - low risk of selection and other biases)
	Additional omm nts: -

Risk of bias

Bias	Authors' judg ment	Support for judgement
Random sequence generation (selection bias)	L w risk	"web-based concealed randomization code".
Allocation concealment (selection bias)	Low isk	"concealed allocation sequence (…) generated by statisticians".
Blinding of particip ts and personnel (perfor mance bias) All outcomes	High risk	"After randomization subjects, physicians and nurses were not blinded to the assigned treatment group.", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"After randomization subjects, physicians and nurses were not blinded to the assigned treatment group.", subjective outcomes reported.

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Toftager 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Eight women were cancelled in the GnRH antagonist group, and 12 in the agonist group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Sudy prospectively registered. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre- and post-2010, prospectively registered. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other bia es detected.

Trenki 2016

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Serbia **Language:** English **Setting:** single centre **Recruitment period:** 2013 to 2014 **Sample size (total randomised):** 90
Participants	**Inclusion criteria:** age 18-39 y ars; BMI 18-30 kg/m^2; PCOS **Exclusion criteria:** uterine an malies; thyroid dysfunction; abnormal prolactin levels; ovarian cysts; male factor infertility **Predicted response as s ted by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertil y:** PCOS **Subg oup (a e):** no **Subgroup BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm :** long agonist plus rFSH (n = 45) **Arm 2:** short antagonist plus rFSH (n = 45) **Fertilisation method:** IVF **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; multiple pregnancy; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript

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Trenki 2016 *(Continued)*

Trial registration: unstated

Registration date: -

Conflict of interest declaration: none declared

Funding: unstated

Author correspondence: yes - trenkic@gmail.com (16 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomizatio list".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"neither the patie ts or the doctors were blinded to the treatment assignment", subject ve outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"neit er the patients nor the doctors were blinded to the treatment assignment", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT nalysis performed. Three cycles cancelled in each group (total = 6).
Selective reporting (reporting bias)	Low ri k	Trial conducted post-2010. Registration details unstated. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted post-2010. Registration status unspecified.

Tshzmachyan 2019

Study character stics

Methods

Design: randomised controlled trial

Country: Armenia

Language: English

Setting: single centre

Recruitment period: unstated

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Tshzmachyan 2019 *(Continued)*

	Sample size (total randomised): 48
Participants	**Inclusion criteria:** age 21-38 years; BMI <25 kg/m^2; PCOS (Rotterdam criteria); AMH >50 pmol/l; no hormonal treatment in the preceding 3 months **Exclusion criteria:** systemic or endocrine disorders; obesity **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH & hMG (n = 24) **Arm 2:** short antagonist plus letrozole & rFSH & h G (n = 24) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** various **Luteal phase support:** freeze-all policy
Outcomes	**Outcomes reported:** live birth; OH S; miscarriage; cancellation; oocyte number **Outcomes included in the meta-a alysis** live birth; OHSS
Notes	**Type of publication:** publish d full xt manuscript **Trial registration:** unstated **Registration date:** **Conflict of inter st d clar tion:** none declared **Funding** no e sought **Auth r corr spondence:** yes - chzmachyan-ruzanna@mail.ru (16 September 2021) **Calculation used to obtain absolute event numbers:** no **In lusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary ou comes [live birth and/or OHSS]) **Ad itional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated list of random numbers".
Allocation concealment (selection bias)	Unclear risk	Unstated.

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Tshzmachyan 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial published post-2010. Registration timeli e unstated. Selective reporting not detected.
Other bias	Unclear risk	Trial published post-2010 Regis ation meline unstated. Single centre study. Recruitment rates unclear as recrui ment timeline unstated.

Tummon 1992

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Canada **Language:** English **Setting:** single centre **Recruitment period:** S ptember 1989 to June 1991 **Sample size (total andom ed):** 508
Participants	**Inclusion criteri** first IVF cycle **Exclu ion cri eria:** <1 million motile sperm in ejaculate **Predicted esponse as stated by the trialists:** unstated **Oocyte donors:** no **Cau e of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** clomifene citrate plus hMG without pituitary suppression (n = 275) **Arm 2:** long agonist plus hMG (n = 233) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** oral micronised progesterone

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Tummon 1992 *(Continued)*

Outcomes	**Outcomes reported:** cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details ot found) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (unclear risk of selec ion bias, h gh risk of other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judg ment
Random sequence generation (selection bias)	Low risk	"sequence of random ed numbers".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Seventy women cancelled in the clomifene group, and eighteen in the agonist group. Attrition >10% in the clomiphene group.
Selective reporting (reporting bias)	ow ris	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	High risk	Trial conducted pre-2010. Single centre study with high recruitment rates. Effect size difference lower than two-fold between trial arms. No other biases detected.

Turkcapar 2013

Study characteristics

Methods	**Design:** randomised controlled trial

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Turkcapar 2013 *(Continued)*

	Country: Turkey
	Language: English
	Setting: single centre
	Recruitment period: January 2008 to December 2008
	Sample size (total randomised): 84
Participants	**Inclusion criteria:** PCOS (Rotterdam criteria)
	Exclusion criteria: age >39 years or serum FSH levels >12mIU/ml; history f ovarian surgery and/or the presence of severe male infertility requiring SSR
	Predicted response as stated by the trialists: predicted high respon e
	Oocyte donors: no
	Cause of infertility: unstated
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 42)
	Arm 2: long agonist plus rFSH (n = 42)
	Fertilisation method: ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported** live birth; OHSS; clinical pregnancy; oocyte number
	Outcomes included in the meta-analysis: live birth; OHSS
Notes	**Type of p licati n:** published full-text manuscript
	Trial egistration: unstated
	Registratio date: -
	Conflict of interest declaration: none declared
	Fund g: "This study was not financially supported by any company or organization"
	Author correspondence: yes - bernaseckin1@hotmail.com (1 April 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Prev

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Turkcapar 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	"computer-generated randomization list".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Unable to extract data from the orig nal manuscript as intention to treat as the authors do not specify to which g oup w men lost to follow-up belonged. Successful correspondence ith A. Turkcapar allowed for clarification and data inclusion. Four women los to follow-u in the hMG group. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre 2010. Single centre study with plausible recruitment rates. No concerns regardin validity of results. Effect size difference lower than two-fold between tr al arms. No other biases detected.

van de-Helder 1990a

Study characteristics	
Methods	**Design:** randomised control ed trial **Country:** The Ne erlands **Language:** English **Setting:** s gle centre **Re ruitment period:** unstated **Sample size (total randomised):** 153
Participants	**Incl sion criteria:** age <41 years; blocked fallopian tubes; regular menstrual cycles; no evidence of pituita y, thyroid or adrenal disease **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** tubal **Subgroup (age):** no **Subgroup (BMI):** no

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van de-Helder 1990a *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** hMG without pituitary suppression (n = 52) **Arm 2:** agonist flare plus hMG (n = 51) **Arm 3:** long agonist plus hMG (n = 50) **Fertilisation method:** unstated **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** hCG and progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; ongoing pregnancy; multiple pregna cy; miscarriage; ectopic pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscr pt **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none und r ken (author contact details not found) **Calculations used to obtai abso ute eve t numbers:** no **Inclusion in meta-analysis:** o (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -

Risk of bias

Bias	Authors' judgem nt	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	U clear isk	Unstated, subjective outcomes reported.
Blinding of outcome s-sessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Nine women were lost to follow-up in group A, 3 in group B and 11 in group C.

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van de-Helder 1990a *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Verpoest 2006

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Belgium **Language:** English **Setting:** single centre **Recruitment period:** January to September 2003 **Sample size (total randomised):** 20
Participants	**Inclusion criteria:** age <39 years; first or second IVF/ICSI trial; use of ejaculated spermatozoa only **Exclusion criteria:** WHO classification groups (I, II or III) of ovulatory disorders; oligomenorrhoea (menstrual cycle >35 days); polymenorrhoea (menstrual cycle <21 days); early follicular phase FSH concentrations ≥15 IU/l; endometriosis American Fertility Society grades III and IV; IVF/ICSI with PGD; BMI ≥28 kg/m^2 **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility** various **Subgroup (age)** no **Subgroup (BMI):** no **Subgroup ethnicity):** no
Interventions	**Arm 1:** short antagonist plus letrozole & rFSH (n = 10) **Arm 2:** short antagonist plus rFSH (n = 10) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** various **Luteal phase support:** hCG
Outcomes	**Outcomes reported:** clinical pregnancy; oocyte number **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** -

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Verpoest 2006 *(Continued)*

Conflict of interest declaration: unstated

Funding: unstated

Author correspondence: yes - willem.verpoest@az.vub.ac.be (16 September 2021)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated randomization list".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however o ly objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated how ver only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT an lysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Tria conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Verpoest 2017

Study characteristi s

Methods

Design: randomised controlled trial

Country: Belgium

Language: English

Setting: single centre

Recruitment period: unstated

Sample size (total randomised): 122

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Verpoest 2017 *(Continued)*

Participants	**Inclusion criteria:** age <40 years; BMI <30 kg/m^2; first PGD treatment; regular menstrual cycles (25-36 days); PGD for monogenic mutations or structural chromosomal abnormalities **Exclusion criteria:** PCOS; endocrine or autoimmune disturbances; endometriosis grade III-IV **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 62) **Arm 2:** short antagonist plus hMG (n = 60) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** oocyte number; f rtilisation rate; embryo number; blastocyst number; clinical pregnancy **Outcomes included in the meta- nalysis** clinical pregnancy; oocyte number
Notes	**Type of publication:** published fu l text manuscript **Trial registration:** NCT0188874 **Registration date:** 28 Ju e 2013 **Conflict of interest eclara ion:** unstated **Funding:** unstat d **Autho corre pondence:** yes - willem.verpoest@uzbrussel.be (11 July 2021) **Calculati s used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Ad itional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence ge era-tion (selection bias)	Low risk	"computer-generated list was used for randomisation with blocks of 4".
Allocation concealment (selection bias)	Low risk	"concealed to the recruiting nurse who made the decision about the allocation by using a series of consecutively numbered sealed opaque envelopes".
Blinding of participants and personnel (perfor-mance bias)	Low risk	Unstated, however only objective outcomes reported.

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Verpoest 2017 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to extract data per woman randomised as not possible to say how many dropped out from each group prior to analysis.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Trial registered prospectively (NCT01888744 Recruitment rate plausible.

Viet 2009

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Vietnam **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomis d):** 336
Participants	**Inclusion criteria:** high risk of l ovarian response **Exclusion criteria:** nstated **Predicted response as ated by the trialists:** predicted low response **Oocyte dono s:** no **Cause f infertility:** low ovarian response **Subgroup (age):** no **Subgroup (BMI):** no **Subgro p (ethnicity):** no
Interventions	**Arm 1:** short agonist flare plus rFSH (n = 145) **Arm 2:** short antagonist plus rFSH (n = 191) **Fertilisation method:** unstated **Embryo age at the time of transfer:** unstated **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** oocyte number; clinical pregnancy **Outcomes included in the meta-analysis:** none

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Viet 2009 *(Continued)*

Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** no (insufficient data in the abstract; a thor contact details not found) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	stated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	U clear whether ITT analysis performed. Attrition unstated.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	Number of sites unclear. No other biases detected.

Vlaisavljevic 2003

Study characteris c

Methods	**Design:** randomised controlled trial **Country:** Slovenia **Language:** English **Setting:** single centre **Recruitment period:** August 1999 to December 2000

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Vlaisavljevic 2003 *(Continued)*

	Sample size (total randomised): 462
Participants	**Inclusion criteria:** age 18-45 years; IVF with or without ICSI; normal menstrual cycles; FSH <15 IU/l on days 2-3 of the cycle; ≤3 previous ART cycles **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH & uFSH (n = 226 **Arm 2:** long agonist plus rFSH & uFSH (n = 236) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** blastocys (day 5+) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** live birth; clini al pregnancy; miscarriage; ectopic pregnancy; oocyte number **Outcomes included in the meta- na ysis** live birth
Notes	**Type of publication:** publish d full text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of inter st d claration:** unstated **Funding:** stated **Auth r correspondence:** yes - vlai@sb-mb.si (16 September 2021) **Calculations used to obtain absolute event numbers:** no **In lusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary o comes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera-tion (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.

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Vlaisavljevic 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Two women cancelled n the antagonist group, and eleven cancelled in the agonist group. Attrition < 0% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010 Sele tive re orting not detected.
Other bias	High risk	Trial conducted pre-2010 S ngle entre tudy with high recruitment rates. Effect size difference lowe than two-f ld between trial arms. No other biases detected.

Vuong 2015

Study characteristics	
Methods	**Design:** randomised controlled tri l **Country:** Vietnam **Language:** English **Setting:** single centre **Recruitment perio :** Oc ob r 2012 to June 2014 **Sample size (to al randomised):** 240
Participants	**Inclusi n crit ria:** ag ≥35 years; BMI <28 kg/m^2; ≤3 previous attempts; GnRH antagonist protocol **Exclus n c iteria:** PCOS; uterine abnormalities/adhesions; endocrine disorders **Predicted response as stated by the trialists:** unstated **O cyte donors:** no **C use o infertility:** unstated **Subgroup (age):** yes (≥35 years) **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 120) **Arm 2:** short antagonist plus rFSH & rLH (n = 120) **Fertilisation method:** unstated **Embryo age at the time of transfer:** cleavage stage (days 2-4)

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Vuong 2015 *(Continued)*

	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** live birth; OHSS; clinical pregnancy; miscarriage; cancellation; oocyte number **Outcomes included in the meta-analysis:** live birth; OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT02244866 **Registration date:** 19 September 2014 **Conflict of interest declaration:** none declared **Funding:** "The study's administrative work was supported by the R search Ce ter for Genetics and Reproductive Health, School of Medicine Vietnam National Unive ity HCMC." **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analy is - includi g all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgeme t
Random sequence generation (selection bias)	Low risk	"computer-generated random number list".
Allocation concealment (selection bias)	Low risk	"treatment allocation was generated by an administration and provided to study st ff in a sealed envelope. A physician enrolled each patient and then, after the patient had signed the informed consent form, a treatment group was assigned by a midwife who had opened the sealed envelope".
Blinding of participants and personnel (performance bias) All outcomes	High risk	open-label", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open-label", subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Lo risk	ITT analysis performed. Eighteen cycles cancelled in the rFSH group and eleven in the rFSH/rLH group. Attrition <10% in both trial arms.
Selective reporting (r porting bias)	High risk	Trial conducted post-2010, retrospectively registered.
Other bias	High risk	Trial conducted post-2010. Retrospectively registered.

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Weckstein 2004

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** unstated **Recruitment period:** unstated **Sample size (total randomised):** 36
Participants	**Inclusion criteria:** age 39-42 years old; first IVF attempt; FSH <10 9 mI /l; BMI <35 kg/m^2 **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** un tated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** yes (≥35 years) **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** agonist flare plus rFSH & h G n = 1) **Arm 2:** short antagonist plus rFS & hMG (n = 18) **Fertilisation method:** unstated **Embryo age at the tim of transfer:** unstated **Luteal phase support:** intramuscular progesterone
Outcomes	**Outcomes repor ed:** clinical pregnancy; ongoing pregnancy; oocyte number **Outcomes in uded in the meta-analysis:** none
Notes	**Type of pu lication:** conference abstract **Tr al registration:** unstated **Regis ration date:** - **Con ict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken (author contact details not found) **Calculations used to obtain absolute event numbers:** yes **Inclusion in meta-analysis:** no (unclear risk of selection and other biases; primary review outcomes not reported) **Additional comments:** -
Risk of bias	

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Weckstein 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes r ported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis not strictly performed b t possible to extract absolute event numbers from percentages. oss to follow up unstated.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Unclear if single or muticentre study, therefore impossible to assess recruitment rates because i eline is unstated.

Weigert 2002

Study characteristics	
Methods	**Design:** randomised control ed trial **Country:** Austria **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 294
Participants	**In lusion criteria:** age 20-39 years; first IVF cycle; normal ovulatory cycles; tubal infertility, male factor, endometriosis grade I-II or unexplained infertility **Exclusion criteria:** chronic medical conditions; irregular cycles; BMI<20 or >30 kg/m^2; FSH >15 IU/l at baseline **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no

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Weigert 2002 *(Continued)*

	Subgroup (ethnicity): no
Interventions	**Arm 1:** clomifene citrate plus rFSH & rLH without pituitary suppression (n = 154) **Arm 2:** long agonist plus rFSH (n = 140) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** OHSS; cancellation; oocyte number **Outcomes included in the meta-analysis:** OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - wilfried.fei h inge @univie.ac.at (16 September 2021) **Calculations used to obtain absolute ev nt numbers:** no **Inclusion in meta-analysis:** yes (sensit vity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS] **Additional comments:** -

Risk of bias

Bias	**Authors' judgemen**	**upport for judgement**
Random sequence generation (selection bias)	Low risk	computer-generated list".
Allocation concealment (selection bias)	Uncl r risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Un lear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detec ion bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Twenty-six cycles cancelled in group A, and 22 in group B. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.

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Weigert 2002 *(Continued)*

Other bias	Unclear risk	Trial conducted pre-2010. Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Westergaard 2001

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Denmark **Language:** English **Setting:** single centre **Recruitment period:** October 1998 to January 2000 **Sample size (total randomised):** 379
Participants	**Inclusion criteria:** age <40 years; normal menstrual cycle (26-32 days); normal pretreatment basal serum concentrations of FSH and LH (<12 IU/l) measured on day 2 **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** lon agon t plus hMG (n = 189) **Arm 2** long agonist plus rFSH (n = 190) **Fertilisati n method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Lute l phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; multiple pregnancy; oocyte number **Outcomes included in the meta-analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - lw@trianglen.dk (16 September 2021)

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Westergaard 2001 *(Continued)*

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random number tables".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes re orted
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis perform Three women cancelled in the hMG group and two women cancel ed in the hMG group. Attrition <10% per trial arm.
Selective reporting (reporting bias)	Low risk	Tria conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Witz 2020

Study characteristics

Methods	**D sign:** randomised controlled trial **Country:** United States of America **Language:** English **Setting:** multicentre **Recruitment period:** August 2015 to February 2018 **Sample size (total randomised):** 620
Participants	**Inclusion criteria:** age 21-35 years; menstrual cycles of 21-45 days; BMI 18-30 kg/m^2; day 2 or 3 serum FSH levels of 1-12 IU/l; total testosterone, prolactin, and thyroid stimulating hormone within normal limits; serum AMH ≥5 ng/ml at screening; predicted high response

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Witz 2020 *(Continued)*

	Exclusion criteria: stage III-IV endometriosis; history of recurrent miscarriage; previous ART failure from low ovarian response; AFC (diameter 2-10 mm) <10 for both ovaries combined and/or use of hormonal contraception <3 months prior to screening **Predicted response as stated by the trialists:** predicted high response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus hMG (n = 310) **Arm 2:** short antagonist plus rFSH (n = 309) **Fertilisation method:** ICSI **Embryo age at the time of transfer:** blastocyst (d y 5+) **Luteal phase support:** vaginal progesterone
Outcomes	**Outcomes reported:** live birth; OHSS; ong ing p egnancy; miscarriage; cancellation; oocyte number; blastocyst number **Outcomes included in the meta-an lysis:** live birth; OHSS; ongoing pregnancy; miscarriage; cancellation; oocyte number; blastocyst n mbe
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT025542 9 **Registration date:** 18 September 2015 **Conflict of interest dec ara on:** "C.A.W. was an investigator in the MEGASET-HR trial. G.S.D. is a full-time employee o Fer ng Pharmaceuticals, Inc. K.J.D. was an investigator in the MEGASET-HR trial. J.K.P. was an in stigator in the MEGASET-HR trial. Y.S. was employed by Ferring Pharmaceuticals, Inc. at the time th t the MEGASET-HR trial was conducted. V.I.Y. is a full-time employee of Ferring Pharmaceutic ls, Inc P.W.H. is a full-time employee of Ferring Pharmaceuticals, Inc.." **Funding:** Supported by Ferring Pharmaceuticals." **Author correspondence:** yes - patrick.heiser@ferring.com (7 April 2021) **Cal ulations used to obtain absolute event numbers:** no **Inc sion in meta-analysis:** yes (primary analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization lists were generated by the study statistician".
Allocation concealment (selection bias)	Low risk	Centrally managed.

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Witz 2020 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open-label trial", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Assessor-blind" trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Attrition rates <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration unde aken p ospectively. Selective reporting not detected.
Other bias	Low risk	Prospectively registered on 18 S ptemb r 2015. First patient recruited on 15 October 2015. Multicent e study. No concerns regarding validity of results. Effect size difference lowe than two-fo d between trial arms. No other biases detected.

Xavier 2005

Study characteristics	
Methods	**Design:** randomised controlled tr l. **Country:** Portugal **Language:** English **Setting:** single centre **Recruitment period** anua y 2002 to January 2003 **Sample size (to l randomised):** 131
Participants	**Inclu ion criteria:** age ≤40 years; day 3 FSH <10 IU/l; ≤3 previous cycles **Exclusion riteria:** unstated **Pr dicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cau e of infertility:** various **bgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 66) **Arm 2:** long agonist plus rFSH (n = 65) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** unstated

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Xavier 2005 *(Continued)*

	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** OHSS; clinical pregnancy; cancellation; oocyte number **Outcomes included in the meta-analysis:** OHSS; clinical pregnancy; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** none undertaken **Calculations used to obtain absolute event numbe** no **Inclusion in meta-analysis:** yes (primary analys - low risk o selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgeme t
Random sequence generation (selection bias)	Low risk	"sequence of compute generated random numbers".
Allocation concealment (selection bias)	Low risk	"Pre-a locatio concealment was assured by an individual strip of black tape rem ved a the time of randomisation".
Blinding of participants and personnel (performance bias) All outcomes	High risk	op st dy", subjective otucomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open study", subjective otucomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. Nineteen women (13 in the antagonist group and 6 in the agonist group) were excluded after randomisation. Attrition >10% in the antagonist group.
Selective reporting (reporting bias)	Low risk	Trial conducted and published pre-2010. Selective reporting not detected.
Other bias	Low risk	Trial conducted pre-2010. Single centre study with plausible recruitment rates. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Xi 2020

Study characteristics

Methods	**Design:** randomised controlled trial

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Xi 2020 *(Continued)*

	Country: China
	Language: English
	Setting: single centre
	Recruitment period: August 2017 to January 2018
	Sample size (total randomised): 260
Participants	**Inclusion criteria:** age ≤ 42 years; AFC >5; basal serum FSH <10 IU/l; first IVF/ICSI cycle
	Exclusion criteria: ovarian cyst; serum oestradiol >100 pg/mL; already ta ing part in another clinical trial; any contraindications to ovarian stimulation treatment; PCOS; end metriosis grade 3 or higher
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** progestogen plus hMG (n = 130)
	Arm 2: long agonist plus hMG (n = 130)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: oral dydrogesterone and vaginal progesterone
Outcomes	**Outcomes reported** OH S (moderate or severe); cancellation; oocyte number; number of cleavage-stage embryos
	Outcomes inclu ed in the meta-analysis: none
Notes	**Type o publi ation:** published full-text manuscript
	Trial reg st ation: ChiCTR-INR-17012089
	Registration date: 17 July 2017
	C flict of interest declaration: none declared
	Fu ding: "This study was supported by the National Nature Science Foundation of China (No. 3177 989, 81501334), and Shanghai Ninth Hospital Foundation of China (JYLJ030)."
	Author correspondence: yes - kuangyp1506@sh9hospital.org, sammy20080228@icloud.com (15 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: no (unclear risk of selection bias [allocation concealment unstated]; primary review outcomes not reported)
	Additional comments: -

Risk of bias

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Xi 2020 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random number".
Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes", unclear if SNOSE.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed, however possible to extract absolute event numbers. Three women in the GnRH agonist long protocol did not complete oocyte retrievals, and six did not have embryo transfer. In the PPOS group, eight women did not have embryo transfer. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Study prospectively registered. Study data openly available online. Selective reporting not detected
Other bias	Low risk	Trial conducted post 2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Xu 2020

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** single centre **Recruitment period:** May 2016 to May 2017 **Sample size (total randomised):** 819
Participants	**Inclusion criteria:** age <40 years; normal menstrual cycle; BMI 18–28 kg/m^2; basal FSH level <10 IU/ml **Exclusion criteria:** donor recipient cycles or frozen-thawed oocyte cycles; PCO (presence of 12 or more follicles in each ovary); low ovarian response AFC <7 follicles or AMH <1.1 ng/ml; hyperprolactinaemia; endometriotic cyst; hydrosalpinx; uterine abnormalities; congenital adrenal hyperplasia; thyroid disease; use of oral contraceptive; testicular sperm extraction or testicular sperm aspiration **Predicted response as stated by the trialists:** predicted normal response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no

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Xu 2020 *(Continued)*

	Subgroup (BMI): yes (<30 kg/m^2)
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 273)
	Arm 2: long agonist plus rFSH (n = 546) - two arms merged (see additional comments)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: various
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** live birth; OHSS; miscarriage; oocyte number; umber o embryos cryopreserved
	Outcomes included in the meta-analysis: live birth; OHSS
Notes	**Type of publication:** published full-text manuscript
	Trial registration: ChiCTR-INR-16008220
	Registration date: 5 April 2016
	Conflict of interest declaration: none declar d
	Funding: "This project was funded by Gran 81571439 from the National Natural Sciences Foundation of China and Grant 2016YFC1000206-5 from t e National Key Research & Development Program of China."
	Author correspondence: yes - zh _gu jin@sina.com (15 September 2021)
	Calculations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/ OHSS])
	Additional comments: P tients were treated either with a GnRH antagonist protocol (n = 273), depot GnRHa protocol (n = 27) or ong GnRHa protocol (n = 273) when referred for their first ART cycle. For the purposes of meta nalysis, the depot and daily GnRH agonist groups were amalgamated.

Risk of bias

Bias	Author ' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated randomization list.".
Allocation concealment (selection bias)	U clear isk	"sealed, unlabelled envelopes", although unclear if SNOSE.
Blinding of parti ipants and personnel (p rfor mance bias) All outcomes	High risk	"Doctors, participants and nurses were not blinded to the treatment assigned." Open trial, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial, subjective outcomes reported.
Incomplete outcome data (attrition bias)	Low risk	ITT analysis undertaken. One women lost to follow-up in the depot GnRH agonist protocol. Attrition rate <10% in all trial arms.

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Xu 2020 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Trial conducted post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Yang 1995

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 42
Participants	**Inclusion criteria:** age <40 years **Exclusion criteria:** unstated **Predicted response as stat d by he trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI)** no **Subgr up (et nicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 25) **Arm 2:** long agonist plus uFSH (n = 17) **Ferti isation method:** unstated **Emb yo age at the time of transfer:** unstated **L teal phase support:** hCG and progesterone
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; miscarriage; ectopic pregnancy **Outcomes included in the meta-analysis:** live birth
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated

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Yang 1995 *(Continued)*

Funding: unstated

Author correspondence: none undertaken (author contact details not found)

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized sequentially", howeve uneven distribution between groups.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only obje tive outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, howe er only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT ana ysis performed. No loss to follow-up.
Selective reporting (reporting bias)	Low risk	T ial conducted and published pre-2010. Selective reporting not detected.
Other bias	Unclear risk	Trial conducted pre-2010.Single centre study. Recruitment rates unclear as study timeline unstated. Effect size difference lower than two-fold between trial arms. No other biases detected.

Yang 1996

Study characteristics

Methods	**Des gn:** randomised controlled trial **Country:** Taiwan **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 60
Participants	**Inclusion criteria:** age <40 years

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Yang 1996 *(Continued)*

	Exclusion criteria: PCO; severe male factor
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** long agonist plus hMG (n = 30)
	Arm 2: agonist flare plus hMG (n = 30)
	Fertilisation method: unstated
	Embryo age at the time of transfer: unstated
	Luteal phase support: hCG and progesterone
Outcomes	**Outcomes reported:** live birth; ongoing pregnancy; multiple pregnancy; miscarriage; ectopic pregnancy; cancellation; oocyte number
	Outcomes included in the meta-analysis: ive bi h
Notes	**Type of publication:** published full ex manuscript
	Trial registration: unstated
	Registration date: -
	Conflict of interest declaration unstated
	Funding: unstated
	Author correspond nce: none undertaken (author contact details not found)
	Calculations use to obtain absolute event numbers: no
	Inclu on in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [l ve birth and/or OHSS])
	Additional co ments: -

Risk of bias

Bias	Aut ors' judgement	Support for judgement
Random sequenc genera-tion (selection b as)	nclear risk	"randomly divided", methodology unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, subjective outcomes reported (e.g. cancellation).

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Yang 1996 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, subjective outcomes reported (e.g. cancellation).
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No attrition reported.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	Single centre study with unclear timeline. Tri l conducted pre-2010.

Yang 2019

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** single centre **Recruitment period:** October 2015 to August 2016 **Sample size (total randomised):** 1 0
Participants	**Inclusion criteria:** age 21-35 y ars; BMI 18-28 kg/m^2; medical indication for IVF treatment; AFC 15-23 **Exclusion criteria:** contraindication to IVF treatment; previous <4 oocytes obtained in IVF cycles; endometriosis; uterine malf rmations; unexplained miscarriages **Predicted respo se stated by the trialists:** predicted high response **Oocyte d rs:** no **Caus of infe tility:** various **Subgroup (ge):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subg oup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus letrozole & rFSH (n = 65) **Arm 2:** long agonist plus rFSH (n = 65) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** unstated
Outcomes	**Outcomes reported:** live birth; OHSS; clinical pregnancy; miscarriage **Outcomes included in the meta-analysis:** live birth; OHSS; clinical pregnancy; miscarriage

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Yang 2019 *(Continued)*

Notes	**Type of publication:** published full-text manuscript **Trial registration:** ChiCTR-IPR-15006211 **Registration date:** 7 April 2015 **Conflict of interest declaration:** none declared **Funding:** none sought **Author correspondence:** yes - gongfeizxxy@126.com (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (primary analysis - low risk of sele tion and o her biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated list".
Allocation concealment (selection bias)	Low risk	"Random numbe ist was generated by research department staff of the hospital and provided t the study nurse in a sealed envelope. (…) the assignment order was hidden u t the research nurse specified the intervention".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Physicia s and e bryologists were blinded to the assignments", unclear whether pa ents were too.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Physicians and embryologists were blinded to the assignments".
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Five women withdrew from group A and one from group B. Attrition <10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Yasa 2013

Study characteristics

Methods	**Design:** randomised controlled trial **Country:** Turkey **Language:** English

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Yasa 2013 *(Continued)*

	Setting: single centre
	Recruitment period: unstated
	Sample size (total randomised): 50
Participants	**Inclusion criteria:** age ≤40 years; normal hormone profile; normal transvaginal ultrasound
	Exclusion criteria: age >40 years; FSH >15 IU/l; AFC <5; BMI >30 kg/m^2; any abnormal ultrasound results (i.e., cyst, endometrioma, endometrial polyp); previous IVF attempts
	Predicted response as stated by the trialists: unstated
	Oocyte donors: no
	Cause of infertility: various
	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus letrozole & rFSH (n = 25)
	Arm 2: short antagonist plus rFSH (n = 25)
	Fertilisation method: unstated
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal proge tero e
Outcomes	**Outcomes reported:** OHSS; linical pregnancy; ongoing pregnancy; oocyte number
	Outcomes included in the met analysis: OHSS
Notes	**Type of publication** pub ished full-text manuscript
	Trial registratio : un tated
	Registra o date
	Conf ct of interest declaration: unstated
	Funding: unstated
	Au hor correspondence: yes - ercan.bastu@istanbul.edu.tr (16 September 2021)
	Calcu ations used to obtain absolute event numbers: no
	Inclusion in meta-analysis: yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])
	Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.

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Yasa 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unstated, however only objective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. No loss to follow p.
Selective reporting (reporting bias)	Low risk	Study published in 2013. R gistr tion st tus unspecified. Selective reporting not detected.
Other bias	Unclear risk	Study published in 2013. R gistration status unspecified. Single centre study. Recruitment rates unclear as study timeline unstated.

Ye 2009

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** single cent e **Recruitment pe iod:** August 2006 to February 2007 **Sample size (otal r ndomised):** 220
Participants	**Inclusio c iteria:** age 25-35 years; BMI 18-25 kg/m^2; <3 previous IVF cycles; no previous low response; normo-ovula ory cycles (24-35 days); both ovaries present; normal uterus; no hormone therapy within the past 3 months; no current or past diseases affecting the ovaries **Ex usion criteria:** unstated **Pre icted response as stated by the trialists:** unstated **Oo yte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** short antagonist plus rFSH (n = 109) **Arm 2:** long agonist plus rFSH (n = 111)

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Ye 2009 *(Continued)*

	Fertilisation method: IVF or ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** injectable progesterone
Outcomes	**Outcomes reported:** live birth; OHSS; clinical pregnancy; miscarriage; oocyte number **Outcomes included in the meta-analysis:** live birth; OHSS
Notes	**Type of publication:** published full-text manuscript **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated **Author correspondence:** yes - yehong1210@163 com (23 February 2022) **Calculations used to obtain absolute event numb rs:** yes **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support f judg ment
Random sequence generation (selection bias)	Low risk	"Ran omiza ion allocation sequence was generated from a table of computer-generated random numbers".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"not blind", subjective outcomes reported (e.g. cancellation).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"not blind", subjective outcomes reported (e.g. cancellation).
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Live birth absolute numbers extracted from percentages. Attrition <10% in both trial arms.
Selective reporting (- porting bias)	Low risk	Selective reporting not detected.
Other bias	Low risk	Single centre study conducted pre-2010, plausible recruitment rates.

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Ye 2012

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** China **Language:** English **Setting:** single centre **Recruitment period:** April 2009 to January 2010 **Sample size (total randomised):** 127
Participants	**Inclusion criteria:** age 35-39 years; BMI 18-25 kg/m^2; first IVF/ICS cycle; norma ovulatory cycles; basal FSH <10 IU/l on day 2-3; both ovaries normal; normal uterus; no hormone therapy within the past 3 months; no current or past diseases affecting the ovaries, g adotrophin, sex steroid secretion, clearance or excretion **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** uns ted **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG = 63) **Arm 2:** long agonist plus rFSH (n 64) **Fertilisation meth d:** IVF o ICSI **Embryo age at the time of transfer:** cleavage stage (days 2-4) **Luteal hase uppor** vaginal progesterone
Outcomes	**Outcom s eported:** live birth; OHSS; clinical pregnancy; ongoing pregnancy; oocyte number; number of embryos yopreserved **O tcomes included in the meta-analysis:** live birth; OHSS
Notes	**ype of publication:** published full-text manuscript **Tria registration:** unstated **Registration date:** - **Conflict of interest declaration:** none declared **Funding:** unstated **Author correspondence:** yes - yehong1210@163.com (16 September 2021) **Calculations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS])

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Ye 2012 *(Continued)*

Additional comments: -

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated random numbers".
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"This was not a blinded study", subjectiv outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"This was not a blinded s udy", subj ctive outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not strictly performed but possible to extract absolute event numbers. Four cycles canc lled in the HP-hMG group (one after oocye retrieval) and seven cancelled in t e rFSH group. Attrition >10% in the rFSH group.
Selective reporting (reporting bias)	Low risk	Study conducted up t 2010 (January). Selective reporting not detected.
Other bias	Low risk	Trial cond ted mostly pre-2010. Single centre study with plausible recruitment ra s. No concerns regarding validity of results. Effect size difference lowe than wo-fold between trial arms. No other biases detected.

Younis 2016

Study characteristics	
Methods	**Design:** rand mised controlled trial **Country:** Is ael **La guage:** English **Setti g:** single centre **Rec itment period:** April 2010 to April 2013 **mple size (total randomised):** 63
Participants	**Inclusion criteria:** age 35-44 years; previous low ovarian response; regular menstrual cycles; two intact ovaries; BMI 18-35 kg/m^2; normal uterine cavity (hysterosalpingography and/or hysteroscopy) **Exclusion criteria:** PCOS; severe endometriosis; uncontrolled thyroid disease; diabetes mellitus; significant hyperprolactinaemia; hypogonadotrophic hypogonadism; >4 previous unsuccessful attempts **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various

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Younis 2016 *(Continued)*

	Subgroup (age): no
	Subgroup (BMI): no
	Subgroup (ethnicity): no
Interventions	**Arm 1:** short antagonist plus rFSH & rLH (n = 32)
	Arm 2: short antagonist plus rFSH (n = 31)
	Fertilisation method: IVF or ICSI
	Embryo age at the time of transfer: cleavage stage (days 2-4)
	Luteal phase support: vaginal progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; oocyte number; number of embryos cryopreserved
	Outcomes included in the meta-analysis: none
Notes	**Type of publication:** published full-text manusc pt
	Trial registration: NCT01016210
	Registration date: 19 November 2009
	Conflict of interest declaration: none de ared
	Funding: ""The authors appreciate and thank Merck-Serono Israel for providing Luveris pro bono to the women participating in the study.
	Author correspondence: yes - jsy@netvis on.net.il (16 September 2021)
	Calculations used to obtain abso ute event numbers: no
	Inclusion in meta-analysis: no unclear risk of selection bias; primary review outcomes not reported)
	Additional comments: -

Risk of bias

Bias	Authors jud emen	Support for judgement
Random sequence generation (selection bias)	Unclea risk	Random and blinded selection of preprepared sealed envelopes, containing cards indicating study or control, was employed.
Allocation concealment (selection bias)	Unclear risk	Random and blinded selection of preprepared sealed envelopes, containing cards indicating study or control, was employed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Participating patients and managing doctors and nurses were aware of the drug regimen", subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"embryologists, endocrine laboratory technicians and ultrasound technicians were blinded to the treatment protocol".
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis not strictly performed but possible to extract absolute event numbers. A total of four women were cancelled, two in each group. Attrition rate <10% in both trial arms.

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Younis 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Youssef 2017

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** Egypt **Language:** English **Setting:** multicentre **Recruitment period:** May 2011 to April 2014 **Sample size (total randomised):** 394
Participants	**Inclusion criteria:** age ≥35 years; low ovaria reserve (FSH >10 IU/l; AFC <5; cycle cancellation during a previous IVF cycle; or previous oocyte yield ≤5 ocytes) **Exclusion criteria:** age >43 years; pre-exis ng medical conditions; congenital uterine anomalies; PCOS; any other causes for anovula on **Predicted response as stated by t e trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** es 35 years) **Subgrou (MI):** no **Subg oup (e hnicity):** no
Interventions	**Arm 1:** shor ntagonist plus rFSH or uFSH (n = 195) **Arm 2:** long agonist plus hMG (n = 199) **Fertili ation method:** unstated **Emb yo age at the time of transfer:** cleavage stage (days 2-4) **Luteal phase support:** vaginal progesterone pessaries or intramuscular progesterone
Outcomes	**Outcomes reported:** clinical pregnancy; ongoing pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number **Outcomes included in the meta-analysis:** clinical pregnancy; ongoing pregnancy; multiple pregnancy; miscarriage; cancellation; oocyte number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NTR2788

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Youssef 2017 *(Continued)*

Registration date: 01 March 2011

Conflict of interest declaration: none declared

Funding: "NUFFIC scholarship (the Netherlands) and STDF short-term fellowship (Egypt, project number: 5445)."

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: yes (primary analysis - low risk of selection and other biases)

Additional comments: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was per ormed wit an online randomization prgram, stratified for study center. A web-based pr gram generated a unique number with allocation code after entry of the pa ient's initials and date of birth".
Allocation concealment (selection bias)	Low risk	"Neither the recruiters nor the trial project group could access the randomization sequence".
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Blinding was not possible owing to the nature of the interventions", subjective outcomes repo te .
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Bli ding was not possible owing to the nature of the interventions", subjective o tcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	I T analysis performed. A total of 52 women were cancelled in the mild stimulation group, while 37 were cancelled in the conventional stimulation group. At rition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010 and registered prospectively. Selective reporting not detected.
Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Multicentre study. No concerns regarding validity of results. Effect size difference lower than two-fold between trial arms. No other biases detected.

Yu 2018

Study characteris ic

Methods	**Design:** randomised controlled trial
	Country: China
	Language: English
	Setting: single centre
	Recruitment period: March 2015 to September 2015

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Yu 2018 *(Continued)*

	Sample size (total randomised): 166
Participants	**Inclusion criteria:** age ≤42 years; BMI <23 kg/m^2; serum FSH ≥15 IU/l or ratio of basal FSH to luteinising hormone ≥3; total AFC ≤8; AMH <1.5 ng/ml; first ART cycle; tubal factor or male factor infertility; no definitive endometriosis, thyroid, adrenal or other endocrine diseases; no history of ovarian surgery **Exclusion criteria:** unstated **Predicted response as stated by the trialists:** predicted low response **Oocyte donors:** no **Cause of infertility:** low ovarian reserve **Subgroup (age):** no **Subgroup (BMI):** yes (<30 kg/m^2) **Subgroup (ethnicity):** no
Interventions	**Arm 1:** long agonist plus hMG (n = 54) **Arm 2:** short antagonist plus letrozole & hMG (n = 52) **Arm 3:** short antagonist plus hMG (n = 60) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** clea ge stage (days 2-4) **Luteal phase support:** IM and PO prog sterone
Outcomes	**Outcomes reported:** live birth; ocyte number **Outcomes included in the me a-analysis:** live birth
Notes	**Type of publication:** p blished full-text manuscript **Trial registration:** r gistere locally **Registration da :** December 2014 **Confli t of in erest declaration:** none declared **Funding** " his research was supported by grants from the National Natural Science Foundation of China (no. 81501382), Zhejiang Provincial Natural Science Foundation of China (no. LQ13H100003) and Wenzhou Science and Technology Bureau Foundation (no. Y20130375)." **Au or correspondence:** yes - peiyu_wang2017@163.com (16 September 2021) **Cal ulations used to obtain absolute event numbers:** no **Inclusion in meta-analysis:** yes (sensitivity analysis - including all studies reporting on the primary outcomes [live birth and/or OHSS]) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random number generation software".

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Yu 2018 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated, subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis performed. A total of six wom n were cancelled in group A, 17 in group B and 10 in group C. Attrition >10% in a l trial a ms.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010 Regis ration ndertaken prospectively, although trial register not accessib e. No evid nce of selective reporting.
Other bias	Low risk	Trial conducted post-2010 nd pros ectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Zhang 2016

Study characteristics	
Methods	**Design:** randomised controll d trial **Country:** United States of Ameri a **Language:** English **Setting:** single centr **Recruitm t peri d:** February 2009 to August 2013 **Samp e size otal randomised):** 564
Participants	**Inclusion cr teria:** age 18-38 years; normal menstrual cycles; first IVF treatment; infertility diagnoses of male, unexplained and tubal factors **Ex lusion criteria:** pre-existing medical conditions (diabetes, hypertension, hypothyroidism, hyperprolact aemia); BMI <18.5 or >32 kg/m^2; day 3 FSH >12 mIU/ml; submucosal or large intramural fibroids requiring surgery **Pr dicted response as stated by the trialists:** unstated **Oocyte donors:** no **Cause of infertility:** various **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicity):** no
Interventions	**Arm 1:** clomifene citrate plus hMG & rFSH & uFSH without pituitary suppression (n = 285)

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Zhang 2016 *(Continued)*

	Arm 2: long agonist plus hMG & rFSH & uFSH (n = 279) **Fertilisation method:** IVF or ICSI **Embryo age at the time of transfer:** blastocyst (day 5+) **Luteal phase support:** freeze-all policy
Outcomes	**Outcomes reported:** live birth; clinical pregnancy; multiple pregnancy; cancellation; oocyte number; blastocyst number **Outcomes included in the meta-analysis:** live birth; clinical pregnancy; multiple pregnancy; cancellation; oocyte number; blastocyst number
Notes	**Type of publication:** published full-text manuscript **Trial registration:** NCT00799929 **Registration date:** 1 December 2008 **Conflict of interest declaration:** unstated **Funding:** "Internal grant funding from New Hope Fe tility Center." **Author correspondence:** yes. Madelon van Welly confirmed via email on 12th July 2022 that women in the conventional IVF group (arm 2) underwent a first fresh or frozen transfer, and that no duplicates were included in the outcome data after the f rst t ansfer. **Calculations used to obtain absolute ev t numbers:** no **Inclusion in meta-analysis:** yes (prima y analysis - low risk of selection and other biases) **Additional comments:** -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated list".
Allocation concealment (selection bias)	Low risk	"Sequentially numbered opaque envelopes".
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Women and staff were not blinded". Subjective outcomes reported.
Blinding of outcome assessment (detecti n bias) All outcomes	High risk	"Women and staff were not blinded". Subjective outcomes reported.
Incomplete outcome d ta (attrition bias) All outcomes	High risk	ITT analysis performed. Six women were cancelled in the mini-IVF arm and 44 had no embryo transfer. In the conventional IVF arm, 20 were cancelled before oocyte retrieval and 22 did not have embryo transfer. Attrition >10% in both trial arms.
Selective reporting (reporting bias)	Low risk	Trial conducted post-2010. Registration undertaken prospectively. All outcomes reported as stated in the registration.

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Zhang 2016 *(Continued)*

Other bias	Low risk	Trial conducted post-2010 and prospectively registered. Single centre study with plausible recruitment rates. Effect size difference lower than two-fold between trial arms.

Zosmer 2004

Study characteristics	
Methods	**Design:** randomised controlled trial **Country:** United Kingdom **Language:** English **Setting:** single centre **Recruitment period:** unstated **Sample size (total randomised):** 30
Participants	**Inclusion criteria:** women undergoing COS for ART **Exclusion criteria:** unstated **Predicted response as stated by the t alists:** unstated **Oocyte donors:** no **Cause of infertility:** unstated **Subgroup (age):** no **Subgroup (BMI):** no **Subgroup (ethnicit):** no
Interventions	**Arm 1:** short ant gonist plus rFSH (n = 10) **Arm 2:** hort ntagonist plus rFSH & rLH concurrently with rFSH or from the day of antagonist commenc ment (= 20) - two arms merged (see additional comments) **Fertilisati n method:** unstated **Embryo age at the time of transfer:** unstated **Lute l phase support:** unstated
Outcomes	**Outcomes reported:** total gonadotrophin dose; oocyte number; fertilisation rate; implantation rate; severe OHSS; ongoing pregnancy **Outcomes included in the meta-analysis:** none
Notes	**Type of publication:** conference abstract **Trial registration:** unstated **Registration date:** - **Conflict of interest declaration:** unstated **Funding:** unstated

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Zosmer 2004 *(Continued)*

Author correspondence: none undertaken

Calculations used to obtain absolute event numbers: no

Inclusion in meta-analysis: no (insufficient data in the abstract; author contact details not found)

Additional comments: thirty women were randomised to a short GnRH antagonist protocol using either rFSH alone (n = 10), rFSH plus rLH from the day of antagonist commencement (n = 10), or rFSH plus rLH concurrently (n = 10). For the purposes of meta-analysis, we planned to amalgamate both groups using rLH.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unstated.
Allocation concealment (selection bias)	Unclear risk	Unstated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unstated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unstated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Selective reporting not detected.
Other bias	Unclear risk	Single centre study. Recruitment rates unclear.

AFC, antral follicle count; AMH, anti-Müllerian hormone; ART, assisted reproductive technology; BMI, body mass index; COS, controlled ovarian stimulation; CPR, clinical pregnancy rate; DHEA, dehydroepiandrosterone; E2, oestradiol; ET, embryo transfer; FET, frozen embryo transfer; FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; GIFT, gamete intrafallopian transfer; GnRH, gonadotrophin-releasing hormone; HBsAg, hepatitis B antigen; HBV, hepatitis B virus; hCG, human chorionic gonadotrophin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hMG, human menopausal gonadotrophin; HP-hMG, highly purified human menopausal gonadotrophin; ICSI, intracytoplasmic sperm injection; IM, intramuscular; ITT, intention to treat; IU, international units; IVF, in vitro fertilisation; LA, leuprolide acetate; MESA, microepididymal sperm aspiration; MR, miscarriage rate; N/A, not applicable; OHSS, ovarian hyperstimulation syndrome; OPR, ongoing pregnancy rate; PCOS, polycystic ovary syndrome; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; POI, premature ovarian insufficiency; POR, poor ovarian response; PV, vaginal route; rFSH, recombinant follicle-stimulating hormone; rLH, recombinant luteinising hormone; RPL, recurrent pregnancy loss; SC, subcutaneous; SFA, seminal fluid analysis; SNOSE, sealed, consecutively numbered opaque envelopes; SSR, surgical sperm retrieval; TESA, testicular sperm aspiration; TESE, testicular sperm extraction; TSH, thyroid-stimulating hormone; uFSH, urinary follicle-stimulating hormone; uLH, urinary luteinising hormone; uhCG, urinary human chorionic gonadotrophin; WHO, World Health Organization; ZIFT, zygote intrafallopian transfer

Characteristics of excluded studies *[ordered by study ID]*

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Study	Reason for exclusion
Abae 2002	High risk of selection bias: "based on the result of the sum of the woman's social security number", therefore inadequate. Study excluded.
Abdalla 1990	Not a randomised trial.
Abd-Elaziz 2017	Wrong population (participants did not specifically present with infertility). None of the outcomes of interest were evaluated in this trial of pharmacokinetic properties. Authors contacted on 24 February 2022 - awaiting reply.
Abdelmassih 2005	Trial comparing different trigger drugs.
Aboulghar 1996	Not a randomised trial.
Aboulghar 2007	Did not evaluate different COS protocol, but rather different stra gies to prevent OHSS.
Abuzeid 2002	Evaluation of two different rFSH formulations hence excluded.
Abuzeid 2012	Trial comparing different timings of commen ing GnRH a tagonist.
Abyholm 2008	Trial evaluating four groups in whom different doses of rFSH were administered.
Acevedo 2006	Trial comparing different ovulation tri ger regimens.
Acharya 1992	Both arms had short flare GnRH agon t protocols.
ACTRN12616001539426 2016	Trial authors contacted and reply bta ned - this trial compared different doses of the same drug (hMG), therefore excluded.
Aflatoonian 2017	Trial comparing delayed s imula on versus immediate stimulation protocol. Therefore excluded.
Akaboshi 1998	Randomisation undertaken by "envelope shuffling", therefore high risk of selection bias. Trial excluded on this basis.
Al-Inany 2001	Commentary paper
Allegra 2006	Thi trial vestig ted women undergoing IUI, excluded on this basis.
Almog 2011	Non ra domised trial.
Alviggi 2003	Trial comparing different doses of the same drug (rLH).
Alviggi 2007	Trial comparing different routes of the same drug.
Alviggi 2013	rial comparing different formulations of the same drug.
Anonymous 1998	Trial comparing different doses of the same drug.
Anserini 2000	Trial comparing different formulations of the same drug.
Antoine 1990	Paper in French. Retrospective study therefore excluded.
Aragona 2016	Same stimulation protocol, the study aimed to assess different embryo transfer timings.
Arce 2005	Pooled analysis of two different studies.

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Study	Reason for exclusion
Arce 2014	Retrospective study.
Arce 2014a	Trial comparing different doses of the same drug.
Arce 2020	Trial comparing different formulations of the same drug.
Ashrafi 2018	Trial comparing delayed start with immediate start in low-responding women.
Atabekoglu 2015	Trial comparing different starting times.
Avrech 1996	Trial comparing different formulations of the same drug (GnRH agonis
Aydogan 2018	Non-randomised: "Eligible patients were assigned seque tia ly to one of the IVF treatments, except patients with PCOS who were assigned to the antagonist protoco exclusively."
Baerwald 2012	Trial comparing the same drug, different start ng times
Balasch 1992	Trial comparing the same drug but different formulation
Barakhoeva 2019	Study comparing follitropin alpha biosimilar versus original follitropin alpha. Therefore the same drug with different formulations.
Bassil 1999	Not a randomised study.
Bassil 2000	Crossover trial.
Bastu 2014	Retrospective study.
Bayoumi 2015	Trial assessing GH vs no GH.
Beckers 2000	Trial comparing the same drug administered with different timings.
Behr 2009	Trial comparing dif eren formulations of the same drug.
Behre 2013	Trial compar g the same drug but different starting time
Behre 2015	T ial comparing the same drug but different starting time
Bellavia 2013	Study co pared different ovulation triggers.
Bensdorp 2015	Trial comparing natural cycle in normal-responding women.
Bentick 1988	Crossover trial.
Berker 2010	Trial comparing different agonist flare protocols, with the addition of GnRH antagonist in one arm.
Bissonnette 2021	Not a randomised study.
Blockeel 2009	Excluded due to high risk of selection bias because of lack of allocation concealment ("concealed to the physician but not to the study nurse").
Blockeel 2011	Trial comparing the same drug but different starting time.
Blockeel 2011a	Trial comparing the same drug but different starting time.

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Study	Reason for exclusion
Blockeel 2014	Trial comparing the same drug but different starting time.
Bonaventura 2004	Trial comparing different doses of the same drug.
Boostanfar 2010	Trial comparing different formulations of the same drug.
Boostanfar 2012	Trial comparing different formulations of the same drug.
Boostanfar 2015	Trial comparing different formulations of the same drug.
Borgato 2016	Crossover trial.
Borges 2004	Trial comparing different formulations of ovulation trigge .
Bosch 2014	Commentary paper.
Bosch 2018	Trial comparing different formulations of the same drug.
Boza 2016	Retrospective observational study.
Brinsden 1998	Two different preparations of rFSH, therefore to exclude.
Brinsden 1998a	Two different preparations of rFSH, ther fore to exclude.
Brinsden 2000	Two different preparations of rFSH, herefore to exclude.
Broekmans 2003	Commentary on the paper by H hmann by the same title.
Camier 1999	Trial comparing different doses of the same drug.
Cedrin-Durnerin 2000	Trial comparing different doses of the same drug.
Cedrin-Durnerin 2006	Trial comparing h sam drug started at different times.
Chang 1991	Not truly rand mised. Participants allocated according to starting day of downregulation/stimula-tio .
Chang 1996	Trial omparing the same drug discontinued at different times.
Chang 2013	Trial comparing the same drug started at different times.
Check 1992	andomization was based on the last digit of the patient's social security number, odd and even numbers receiving short and long protocols respectively", thus not truly randomised.
Check 1995	Not randomised - "last digit of year of birth".
Check 2001	Commentary paper.
Check 2001a	Not truly randomised.
Chen 2018	Retrospective study.
Chen 2019	High risk of selection bias as confirmed by the authors, therefore excluded.
ChiCTR2000031843 2019	Trial comparing different doses of the same drug (rLH 75 IU versus 150 IU).

Preview

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Study	Reason for exclusion
ChiCTR-OPN-14005276 2014	"Observational study, non-randomised" as per trial registry entry: https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-OPN-14005276
Choavaratana 2015	COS undertaken only in one study arm.
Choi 2004	Retrospective study.
Choi 2005	Observational study, not randomised.
Christin-Maitre 2001	Ovulation induction.
Christin-Maitre 2003	Trial comparing different doses of the same drug.
Coelingh-Bennink 1998	Women undergoing ovulation induction.
Contreras-Bretherton 1999	Article in Spanish. Retrospective study, therefore excluded.
Corifollitropin Alfa Dose-finding Study Group 2008	Trial comparing different doses of the same drug.
Corifollitropin Alfa Ensure Study Group 2010	Same drug but different doses.
D'Amato 2004	Excluded as quasi-randomised trial confirmed by the authors on 16 September 2021.
Dakhly 2016	Adjuvant growth hormone administered in all groups.
Dalal 2014	Trial comparing intervention to prevent OHSS (cabergoline).
Daya 2001	Not a randomised trial therefore excluded.
De Placido 2004	Trial comparing different doses of the same drug.
Devroey 2004	Trial comparing different formulations of the same drug.
Devroey 2009	Trial comparing different formulations of the same drug.
Devroey 2015	Retrospective analysis.
Dhont 1995	Women undergoing IVF/GIFT and ZIFT.
Dicker 1991	Trial comparing different formulations of GnRH agonist.
Dirnfeld 1999	same drug administered at different times.
Ditkoff 1996	"Patients were randomly assigned by tossing a coin". High risk fo bias, therefore excluded.
Driscoll 2000	Trial comparing different drugs to trigger ovulation.
During 1999	Trial comparing different formulations of the same drug.
Dzik 2004	RCT comparing different doses of the same drug.
Engel 2002	Initially planned as a randomised trial but then changed to non-randomised.

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Study	Reason for exclusion
Engmann 1998	Trial comparing different routes of the same drug.
EUCTR2004-004771-11-BE 2006	Trial comparing different formulations of the same drug.
EUCTR2009-012847-40-GB 2009	Trial comparing the same antagonist but different starting time. Therefore excluded. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-012847-40-GB
EUCTR2010-019287-37-GB 2010	Trial comparing the same drug but different formulations.
EUCTR2012-001708-39-BE 2012	Trial comparing different formulations of the same drug (rFSH).
EUCTR2012-003227-38-GB 2013	Trial comparing different doses of the same drug
EUCTR2013-002979-17-ES 2013	Trial ended prematurely without data collect on: www.w o.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-002979-17-ES
EUCTR2013-003788-67-AT 2014	Trial comparing different formulations of he same drug.
EUCTR2020-004329-21-IT 2021	Trial comparing different formulat ns of he same drug (rFSH).
Fasouliotis 2003	Retrospective study.
Fatemi 2012	Trial comparing different fo mulations of the same drug.
Fatemi 2017	Trial comparing different formulations of the same drug.
Fauser 2011	Trial comparing iffe nt formulations of the same drug.
Fouda 2011	Trial investig ting prolonged vs short administration of letrozole in an antagonist cycle, therefore excluded.
Fujii 1997	T al com aring agonist stopped early vs stopped until the day before hCG administration.
Galindo 2009	Article Spanish. Retrospective study, therefore excluded.
Garcia-Velasco 2000	Trial comparing different administration timing of the same drug.
Garcia-Velasco 2007	Allo ation "not concealed", therefore high risk of selection bias. Trial excluded on this basis.
Garcia-Velasco 201	rial comparing different timings of antagonist administration, therefore excluded.
Geber 2001a	Study comparing different formulations of the same drug (depot vs daily administration of GnRH agonist).
Gerli 1999	Trial comparing different formulations of the same drug.
Gerli 2013	Article withdrawn by the journal: https://pubmed.ncbi.nlm.nih.gov/23884831/
Ghaffari 2020	The flare-up protocol was similar except that buserelin was administered at a daily dose of 500 µg.

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Study	Reason for exclusion
Gibreel 2012	Review paper.
Giles 2004	Trial comparing different formulations of the same drug.
Gizzo 2015	Trial comparing different doses of the same drug.
Gleicher 2016	Letter to the editor.
Gocial 2000	Trial comparing different formulations of the same drug.
Gomes 2007	Excluded because of high risk of selection bias as confirmed by the auth rs.
Gómez-Palomares 2005	"No concealment of treatment allocation", therefore high ris of selection bias. Excluded on this basis.
Gonen 1991	Non-randomised study.
Griesinger 2020	Trial comparing different doses of the same d ug.
Guivarc'h-Leveque 2010	High risk of selection bias: "patients were randomised according to the day (even or odd) of consultation". Excluded on this basis.
Gunaydin 2007	Trial comparing different administration timing of the same drug.
Hamdine 2013	Trial comparing different administr tion timing of the same drug.
Hamdine 2013a	Trial comparing different admi strati n timing of the same drug.
Havelock 2017	Trial comparing different oses o the same drug.
Hillensjo 2009	Trial comparing different formulations of the same drug.
Hillensjo 2011	Trial comparing dif eren formulations of the same drug.
Hodgen 1996	Review paper
Hong 2001	Quasi-ra domised trial.
Hosseinisadat 2017	Trial comparing different administration timing of the same drug.
Hossein Rashidi 2015	Trial comparing different administration timing of the same drug.
Hreinsson 2003	In vitro maturation trial.
Hubbard 2016	Post-hoc analysis.
IRCT201108116420N 011	Trial comparing different formulations of the same drug (GnRH agonist).
IRCT201409301556N 2014	Trial investigating OCP versus long GnRH agonist administration in women with moderate to severe endometriosis.
IRCT20150105020558N3 2021	Trial investigating interventions in women undergoing FET.
IRCT20190609043845N 2019	Trial comparing different formulations of the same drug (GnRH agonist).

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Study	Reason for exclusion
Ismail 2002	Non-randomised trial.
ISRCTN98623456 2012	Study stopped due to lack of funding, no results reported.
Jie 2005	Trial comparing different ovulation triggers.
Jinno 2009	Study comparing different timing of the same drug (GnRH agonist).
Kamath 2017	Systematic review.
Kannan 1999	Trial comparing two different regimens of ovulation induction Not IVF
KCT0000157 2011	Trial comparing different timings of the same drug (GnRH antagonist).
Keye 2004	Trial comparing different doses of the same drug
Khani 2012	Trial comparing different trigger drugs (rhCG versus uhCG
Kim 2009a	Trial comparing different doses and administration timing of the same drug.
Kim 2013	Trial comparing different doses and administration timing of the same drug.
Kolibianakis 2011	Trial comparing different administration timing of the same drug.
Kolibianakis 2014	Trial comparing different formulations of the same drug.
Kondaveeti 1996	Trial comparing different administration timing of the same drug.
Kong 2018	Study protocol.
Konig 2014	Commentary paper
Koundouros 2008	Trial comparing different doses of the same drug.
Kovanci 2010	Review paper
Kucuk 2007	Trial comparing different administration timing of the same drug.
Kucuk 2008	Trial comparing different administration timing of the same drug.
Lahoud 2010	Trial comparing different doses of the same drug.
Lahoud 2017a	Trial comparing different doses of the same drug.
Larsen 1990	Patients served as their own controls.
Lawrenz 2021	Trial comparing different doses of the same drug.
Leader 2013	Trial comparing different formulations of the same drug.
Levi-Setti 2006	Authors contacted. Reply from main author: "Was allocation concealment performed, and if so, how? NO", therefore excluded due to high risk of selection bias.
Lin 2013	Trial comparing different administration timing of the same drug.

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Study	Reason for exclusion
Loutradis 2004	Non-randomised study.
MacDougall 1992	Natural cycle not specifically in low-responding women.
MacDougall 1994	This trial compared clomid with natural cycle, but not specifically in low-responding women, therefore excluded.
Maged 2015	Trial comparing different administration timing of the same drug.
Maged 2018	Trial comparing different administration timing of the same drug.
Mansour 2003	Non-randomised trial.
Marcus 1993	High risk of selection bias - "randomized by medical file umber, dd numbers to the long protocol and even numbers to the ultra-short protocol". Excluded on this basis.
Mardesic 2011	Trial comparing different formulations of the same drug.
Maroulis 1991	High risk of selection bias - "Patients were rando ized by alternating between protocols in the order that patients called to announce to the nurse coordinator their intention to participate in the next IVF cycle". Excluded on this basis.
Marrs 2003	Trial comparing different dosages of the same drug combination (uFSH and hMG).
Martinez 2003	Authors confirmed no allocation c cealment, therefore to exclude because of high selection bias.
Melo 2009	Trial comparing different ovula ion triggers.
Merviel 2015	High risk of selection bias "rand mization according to the order of entry into the study". Excluded on this basis.
Mochtar 2017	Review paper.
Muasher 1991	Trial compa ng d ferent timings of the same drug.
Murber 2011	Ret ospe tive st dy.
NCT01319695 2011	Tria comparing different formulations of the same drug (rFSH).
NCT01599494 2012	Trial comparing different rFSH formulations.
NCT01687712 2012	ttps://clinicaltrials.gov/ct2/show/NCT01687712. Status: Completed as of 5 December 2017. Comparing two different recombinant forms of FSH, therefore excluded.
NCT02471677 2015	Trial comparing different formulations of the same drug (rFSH).
NCT02477566 2015	Trial comparing two different formulations of the same drug (GnRH agonist).
NCT02681536 2016	https://clinicaltrials.gov/ct2/show/NCT02681536. Status: recruiting as of 4 April 2016. No published data found. Authors emailed and replied: "Thanks for your interest in the study. Unfortunately that study was not published and no results available." on 16 September 2021.
NCT03423537 2019	www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-005208-24-GR. Author contacted and replied on 20 September 2021 - not an RCT.

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Study	Reason for exclusion
NCT03809221 2019	Study comparing different timing of the same drug (GnRH agonist administered in a long protocol to achieve pituitary downregulation).
NCT03940807 2019	Study comparing ultralong versus long GnRH agonist protocol for women with adenomyosis.
NCT04178135 2019	Study comparing different timings of the same drug (rLH).
NCT04385342 2020	Study comparing different timings of the same drugs (FSH continued for different durations).
NCT05103228 2021	Trial comparing different doses of the same drug (rFSH or hMG)
Neyro 1995	Article in Spanish. Same stimulation drugs but different timing.
Nyboe Andersen 2016	Trial comparing different doses of the same drug.
Nyboe Andersen 2017	Trial comparing different formulations of the same drug
Obruca 2010	Trial comparing different formulations of the ame drug
Out 1997	This is a paper including the results of Out 1995 (included), Hedon 1995 (full text not found) and Out 1996 (systematic review).
Papanikolaou 2019	Trial comparing different formulations of the same drug.
Pellicer 1989	GnRH agonist started at different ti es of the cycle to achieve pituitary suppression after 14 days. Excluded based on compariso be we n different administration timing of the same drug.
Polinder 2008	This is a cost-effectiveness an lysis of Heijnen 2007 (whose authors have been emailed for more details about gonadotrop ns before inclusion).
Pu 2011	Review paper.
Rettenbacher 2015	Trial comparing dif eren formulations of the same drug.
Revelli 2012	Trial compar g different administration timing of the same drug.
Reyftmann 2006	S udy comparing different doses of GnRH antagonist, therefore excluded.
Rezaeian 2016	This compares agonist stop with long agonist protocol. All started in the luteal phase. Excluded on the basis of different timings of administration.
Rodriguez 2003	Trial comparing different doses of the same drug.
Rombauts 1998	ome patients in this trial underwent GIFT, not IVF-ET.
Ron El 1990	GnRH agonist was administered in both groups to achieve pituitary downregulation, although the timing of commencement was different.
Ron El 1991	There is a crossover element to this trial where some patients were allocated to the oppositve intervention arm in a subsequent cycle.
Rose 2015	Non-randomised study.
Sagle 1991	Patients were women undergoing ovulation induction for PCOS, therefore excluded.

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Study	Reason for exclusion
Saha 2020	This trial investigated women undergoing IUI, therefore excluded.
Salat Baroux 1988	Trial comparing different administration timing of the same drug.
Sanverdi 2017	Retrospective study.
Sbracia 2012	Trial comparing different formulations of the same drug.
Schoolcraft 2008	Non-randomised study.
Selman 2016	Trial comparing different formulations of the same drug.
Shahrokh Tehrani Nejad 2008	Trial comparing different administration timing of the same drug.
Siristatidis 2017	Case-control study.
Song 2016	Review paper.
Stadtmauer 2005	Participants were undergoing ovulation inductio , IVF.
Strohmer 1997	Trial comparing different agonist flare pro ocols.
Strowitzki 2016	Trial comparing different formulations of the same drug.
Tan 2013	Review paper.
Tandulwadkar 2022	"eligible women were allocated lternatively", therefore excluded on the basis of high risk of selection bias.
Tarlatzis 1993	Women undergoing ZIFT inc uded.
Tarlatzis 2012	Trial comparing diffe ent formulations of the same drug.
Tazegul 2008	Excluded be ause of high risk of selection bias - "sequence of allocation not concealed".
Thakur 2015	Trial com aring d fferent administration timing of the same drug.
Thong 2016	Trial omparing different administration timing of the same drug.
Tulppala 1999	Trial comparing different formulations of the same drug.
Vauthier Brouzes 1993	T ial comparing different formulations of the same drug.
Vuong 2017	rial comparing different formulations of the same drug.
Wang 2016	Crossover trial, therefore excluded.
Warne 2000	Trial comparing different ovulation trigger drugs.
Weissman 2003	Participants underwent zygote intrafallopian transfer.
Weissman 2005	Trial comparing different administration timing of the same drug.
Westergaard 1996	Patients allocated on the basis of menstruation date, hence excluded due to high selection bias.

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Study	Reason for exclusion
Xiao 2019	Retrospective study.
Yang 1991	Full text not found, however the abstract states that tubal embryo transfer was undertaken in almost half the participants, therefore excluded.
Ye 2001	Quasi-randomised study, therefore excluded.
Youssef 2008	Retrospective study.
Yu 2018a	Trial comparing different formulations of the same drug.
Zahiri 2019	Trial comparing different formulations of the same drug.
Zarei 2018	Trial comparing different administration timing of the same drug

COS, controlled ovarian stimulation; ET, embryo transfer; FET, frozen embryo t ansfer; FSH follicle stimulating hormone; GH, growth hormone; GIFT, gamete intrafallopian transfer; GnRH, gonadotrophin releasing ormone; h G, human chorionic gonadotrophin; hMG, human menopausal gonadotrophin; IUI, intrauterine insemination; IVF, in vitro fe ilisatio ; OCP, oral contraceptive pill; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome; RCT, randomised controlled trial; rFSH, recombinant follicle stimulating hormone; rhCG, recombinant human chorionic gonadotrophin; rLH, recomb ant luteinising hormone; uFSH, urinary follicle stimulating hormone; uhCG, urinary human chorionic gonadotrophin; ZIFT, zygote intrafallopian transfer;

Characteristics of studies awaiting classification *[ordered by study ID]*

ACTRN12612000294853 2012

Methods	Randomised controlled tri l
Participants	**Inclusion criteria:** normal uterine anatomy; tubal factor and/or male or unexplained infertility >2 years; basal FSH 2-12 IU/l; BM <35 kg/m^2
Interventions	**Arm 1:** HP-hMG pitu tar downregulation unclear) **Arm 2:** rFSH pituita y downregulation unclear)
Outcomes	Clinical p gnancy; OHSS
Notes	www who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12612000294853 No published data found for this trial. Authors last contacted on 15 September 2021 (yavuzay@istanbul.edu.tr), response awaited.

ACTRN12612000731897 2012

Methods	Trial design unstated
Participants	**Inclusion criteria:** age 18-39 years; ultrasound evidence of polycystic ovarian morphology (POM) without clinical manifestation of PCOS
Interventions	**Arm 1:** long agonist plus highly purified hMG (IM) **Arm 2:** long agonist plus recombinant FSH (SC)
Outcomes	Clinical pregnancy; OHSS; oocyte number

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ACTRN12612000731897 2012 *(Continued)*

Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12612000731897 Trial design unclear. No published data found for this trial. Authors last contacted on 15 September2021 (deveer3@hotmail.com), response awaited.

ACTRN12614000025639 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-35 years; PCOS; normal SFA **Exclusion criteria:** previous pelvic surgery; endometriosis; previous failed ICSI
Interventions	**Arm 1:** letrozole and hMG (pituitary downregulation un ear) **Arm 2:** hMG alone (pituitary downregulation unclear)
Outcomes	Clinical pregnancy; embryo number; oocyte n mber
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12614000025639 No published data found for this trial. Autho s contacted on 09 February 2021 (galal_af@yahoo.com), response awaited.

ACTRN12619001593123 2019

Methods	Trial design unstated
Participants	**Inclusion criteria:** age 21-42 years; low-responding women as per Poseidon criteria (Subgroup 2a and groups 3 an 4); MI 18-35 kg/m^2 **Exclusion cri er** oocyte cryopreservation cycles; severe male factor (concentration <1 million/mL); previous cancer treatment or any other exogenous factor affecting ovarian function; PCO or PCOS ccord ng to Rotterdam criteria; significant preexisting physical or mental health condition; inab ity to consent
Interventions	Unsta d
Outcomes	Unstated
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12619001593123 tatus: not yet recruiting as of 3 March 2022

Agustina 2013

Methods	Randomised controlled trial
Participants	Women undergoing IVF
Interventions	**Arm 1:** GnRH agonist plus rFSH **Arm 2:** GnRH agonist plus hMG

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Agustina 2013 *(Continued)*

	Arm 3: GnRH agonist plus rFSH plus hMG **Arm 4:** GnRH antagonist plus rFSH plus hMG
Outcomes	Review outcomes not reported
Notes	Timing of GnRH analogues unclear. Unclear whether trial assessed outcomes of interest, therefore awaiting classification. No contact details found.

Aizpurua 2015

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** oocyte donors
Interventions	**Arm 1:** short antagonist plus clomifene citrat plus rFSH **Arm 2:** short antagonist plus rFSH (?unclear if clomifene also used in this arm)
Outcomes	Oocyte number; blastocyst number; number of embryos cryopreserved
Notes	Additional details about methodology (e g. dosages, timings, risk of bias) are required. Author contact details not found.

Akarsu 1999

Methods	Trial design unstated
Participants	**Inclusion criteria:** women with previous low response
Interventions	**Arm 1:** minidos long protocol GnRH analogues with uFSH/hMG (details unclear) **Arm 2:** co-f re short protocol (details unclear) with uFSH/hMG
Outcomes	Cancellat on; oocyte number; embryo number; clinical pregnancy
Notes	Method logical data missing. Author contact details not found.

Alam 2010

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-35 years; BMI 18-26 kg/m^2; AFC >10; oocyte donor
Interventions	**Arm 1:** long agonist with rFSH, uFSH or hMG **Arm 2:** short antagonist with rFSH, uFSH or hMG
Outcomes	Oocyte number; cancellation rate
Notes	Insufficient information from abstract to include. Author contact details not found.

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Alama 2016

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-35 years; weight <60 kg; oocyte donors; AFC ≥6 per ovary **Exclusion criteria:** AFC <6 or >20; comorbidities that may interfere with COS treatment
Interventions	**Arm 1:** rFSH (pituitary downregulation unclear) **Arm 2:** HP-hMG (pituitary downregulation unclear) **Arm 3:** rFSH (corifollitropin alpha) (pituitary downregulatio unclear)
Outcomes	Oocyte number; cancellation
Notes	https://clinicaltrials.gov/ct2/show/NCT02213627 Status: unknown, last updated on 17 July 2015 Authors contacted on 17 February 2021 (anton o.requen @ivi.es), response awaited.

Al-Juboory 2020

Methods	"Comparative prospective study"
Participants	Women undergoing ART
Interventions	**Arm 1:** clomifene plus rFSH (pi itary downregulation unclear) **Arm 2:** letrozole plus FSH (pituitary downregulation unclear)
Outcomes	Review outcom s not reported
Notes	Unclear if RCT. No co tact details in the manuscript.

Allaert 1998

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract text not found

Al-Mousawi 2019

Methods	Trial design unstated

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Al-Mousawi 2019 *(Continued)*

Participants	**Inclusion criteria:** women undergoing ICSI
Interventions	**Arm 1:** GnRH agonist (timing and duration unstated) **Arm 2:** GnRH antagonist (timing and duration unstated)
Outcomes	Oocyte number; embryo number
Notes	Unclear if RCT. Authors contacted on 16 September 2021 (hayder.adnan2010@gmail.com), response awaited.

Alvarez 1993

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract ext no found

Anderson 2014

Methods	Randomised controlled tr al
Participants	**Inclusion criteria:** age 21-40 years; anti-Mullerian hormone >1 ng/ml
Interventions	**Arm 1:** GnRH an agonist ("human-derived gonadotrophins", however not specified) **Arm 2:** long GnRH agonist protocol(("human-derived gonadotrophins", however not specified)
Outcomes	O cyte number
Notes	Unable to extract enough information to include study based on abstract. No contact details provided.

Anderson 2018

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 21-41 years; anti-Mullerian hormone >1.0 ng/ml; FSH <10 IU/ml; LH <12 IU/mL; oestradiol <50 pg/ml; AFC 10-20; body weight >50 kg; BMI >18 and <32 kg/m^2
Interventions	**Arm 1:** rFSH (pituitary downregulation unclear) **Arm 2:** HP-hMG (pituitary downregulation unclear)
Outcomes	Oocyte number; number of blastocysts cryopreserved

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Anderson 2018 *(Continued)*

Notes	Data on review outcomes not reported. No contact details for authors.

Anonymous 1998a

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract text not found

Anonymous 2003

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unc ear
Notes	bstract text not found

Antoine 1993

Methods	Randomised controlled trial
Participants	**In lusion criteria:** age <38 years; normo-ovulatory; tubal or idiopathic infertility; normal SFA
Interventions	**Arm 1** HRH agonist plus FSH ± hMG (step-up / step-down) **Arm 2:** FSH ± hMG alone (step-up / step-down)
Outcomes	R view outcomes not reported.
Notes	Article in French. Insufficient data from manuscript regarding stimulation protocols. No up-to-date contact details for authors

Antoine 1997

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <38 years; normo-ovulatory; tubal or idiopathic infertility; normal SFA
Interventions	**Arm 1:** LHRH agonist plus rFSH (step-up / step-down)

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Antoine 1997 *(Continued)*

	Arm 2: rFSH alone (step-up / step-down)
Outcomes	Unstated
Notes	Article in French. Insufficient details of stimulation protocols and outcomes. No up-to-date contact details for authors.

Aragona 2003

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract text not found

Asimakopoulos 2006

Methods	Trial design unstated
Participants	Women undergoing ART
Interventions	**Arm 1:** multidose GnRH a tagonist protocol **Arm 2:** long GnRH agon t pr tocol
Outcomes	Review outcom s not re orted
Notes	Unclear if this was a randomised trial and whether outcomes of interest were reported. Emailed nnikol tos@hotmail.com but bounced back on 19 February 2021. Therefore awaiting classifica-tio .

Awwad 1998

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract text not found

Prev

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Azem 2010

Methods	Randomised controlled study
Participants	Women undergoing ART
Interventions	**Arm 1:** short GnRH agonist protocol plus rFSH **Arm 2:** long GnRH agonist protocol plus rFSH
Outcomes	Clinical pregnancy; live birth
Notes	Detail on stimulation protocols and outcome data lacking. No contac details for authors.

Baart 2012

Methods	Randomised controlled trial
Participants	Women undergoing COS
Interventions	**Arm 1:** mild stimulation regimen and GnRH antagonist co-treatment **Arm 2:** high-dose gonadotrophin regimen a d GnRH agonist co-treatment
Outcomes	Oocyte number
Notes	Unable to extract data from abstract (e g., gonadotrophins unstated). No contact details found.

Bar 2004

Methods	Randomised controlled trial
Participants	Women unde goi g routine COS (n = 24)
Interventions	**Arm 1:** u SH (pi uitary downregulation unclear) **A m 2:** r SH (pituitary downregulation unclear)
Outcomes	Review ou comes not reported.
Notes	No report on clinical outcomes. Pituitary downregulation unclear. Authors emailed 25 February 20 2 reply awaited.

Batiza 1999

Methods	Randomised controlled trial
Participants	Women undergoing ICSI
Interventions	**Arm 1:** rFSH (pituitary downregulation unclear) **Arm 2:** HP-FSH plus hMG (pituitary downregulation unclear)

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Batiza 1999 *(Continued)*

Outcomes	Oocyte number; number of embryos cryopreserved
Notes	No denominator specified for each group, therefore unable to extract data. No contact details for authors.

Batzofin 2002

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-39 years; regular menstrual cycles
Interventions	**Arm 1:** Long GnRH agonist plus rFSH (n = ?) **Arm 2:** Short GnRH antagonist plus rFSH (n = ?)
Outcomes	Review outcomes not reported
Notes	Randomisation numbers unstated. Author contact details not found.

Belaisch 1986

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract text not found

Bessho 1990

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract text not found

Borges 2005

Methods	Unclear
Participants	**Inclusion criteria:** age 25-35 years; BMI 18-29 kg/m^2; basal FSH <10 mIU/ml; regular cycles

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Borges 2005 *(Continued)*

Interventions	**Arm 1:** Short GnRH antagonist plus rFSH **Arm 2:** Short GnRH antagonist plus rFSH and rhCG
Outcomes	Oocyte number; number of embryos cryopreserved
Notes	Unclear if this study is randomised. No contact details for the authors.

Borini 1995

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract text not found

Buvat 1991

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <38 y ars
Interventions	**Arm 1:** long GnRH agonist p otocol plus hMG **Arm 2:** short GnRH ag nist flare protocol plus hMG
Outcomes	Insufficient d ta ailable
Notes	Insu ficie t data in the abstract for extraction

Buvat 1993

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract text not found

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Causio 2004

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <35 years; tubal factor infertility
Interventions	**Arm 1:** GnRH agonist (duration unstated) **Arm 2:** GnRH antagonist
Outcomes	Clinical pregnancy
Notes	No details of gonadotrophins used for COS and duration of GnRH ago ist administration, therefore not possible to include. Author contact details not found.

Cedrin-Durnerin 1992

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Ab act text not found

Cedrin-Durnerin 1993

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract text not found

Cedrin-Durnerin 2004a

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract text not found

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Celik 2011

Methods	Unclear
Participants	**Inclusion criteria:** primary or secondary women with major indications for IVF; age 20-40 years; BMI 18-29 kg/m^2; regular menstrual cycles ranging from 25 to 35 days; normal basal serum FSH (<13 IU/l) and oestradiol (<75 pg/ml) levels determined on day 3 of the cycle; normal basal serum TSH and prolactin; no uterine, ovarian or adnexal pathology diagnosed by transvaginal ultrasound **Exclusion criteria:** history of recurrent pregnancy loss; previous OHSS; previous unsuccessful fertilisation; PCOS; severe endometriosis; systemic disease; endocrine or metabolic disorder
Interventions	**Arm 1:** long GnRH agonist plus rFSH **Arm 2:** long GnRH agonist plus HP-hMG
Outcomes	Ongoing pregnancy; oocyte number
Notes	Unclear whether the study was prospective a d random sed. Author contacted (cemcel@yahoo.com) on 16 February 2021, reply awaited

Check 2003

Methods	Unclear - "the choice of regimen was random but not prospective"
Participants	**Inclusion criteria:** age >40 yea s or previous low response
Interventions	**Arm 1:** long GnRH agonist (stop protocol) **Arm 2:** microdose GnRH agonist lare
Outcomes	Clinical pregnancy
Notes	Abstract contai s insuffi ient information on gonadotrophins used. Author contact details not found.

Check 2003a

Methods	Unclear
Participants	**Inclusion criteria:** previous low response; baseline FSH >12 mIU/ml
Interventions	**Arm 1:** natural cycle IVF **Arm 2:** minimal stimulation (details unstated)
Outcomes	Number of embryos cryopreserved; ongoing pregnancy; clinical pregnancy
Notes	Insufficient data in the abstract for extraction. No contact details for the authors.

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Chedid 2005

Methods	Unstated
Participants	Women undergoing ART
Interventions	**Arm 1:** rFSH (details of downregulation unstated) **Arm 2:** rFSH plus rLH (details of downregulation unstated)
Outcomes	Oocyte number
Notes	Insufficient data in the abstract to include. Author contact details not found.

Cheung 1999

Methods	Prospective study, unclear if randomised
Participants	**Inclusion criteria:** ovulatory women with un xplained in ertility
Interventions	**Arm 1:** rFSH (variable downregulation regimens) **Arm 2:** rFSH and rLH (variable downregulat on regimens)
Outcomes	Review outcomes not reported.
Notes	Insufficient data in the abstract for xtraction. No author contact details found.

ChiCTR1800015574 2018

Methods	Randomised controlled trial
Participants	**Inclusion cri eria** age 20-38 years; tubal factor, male factor or ovulation disorder other than poly-cystic ovary yndrome; ≥1 year of infertility; normal ovarian reserve (basal FSH < 10mIU/ml, AFC 8-15 1.5 AMH 4.0 ng/ml); menstrual regularity, defined as the menstrual cycle 21-35 days; BMI 18 5-24 kg m^2; first IVF/ICSI-ET treatment **Exclu on criteria:** contraindications to assisted reproductive technology or contraindications to pregna cy; uterine abnormalities judged by clinical experience, such as uterine malformations (unicornuate uterus, bicornuate uterus, double uterus, septate uterus); adenomyosis; patients with uterine fibroids (fibroids larger than 3 cm or submucosal uterine fibroids; intrauterine adhesions; u treated endometrial polyps; scarred uterus; frozen embryo transfer; hydrosalpinx, PGD or PGS patients; recurrent miscarriage; polycystic ovary syndrome; endometriosis stage III-IV; unilateral ovary; chromosomal abnormalities in either partner; people with alcoholism, smoking, drug abuse habit; patients participating in other clinical studies
Interventions	**Arm 1:** "ultra-long early follicular phase" **Arm 2:** "antagonist regimen"
Outcomes	Live birth; clinical pregnancy; OHSS; miscarriage; ectopic pregnancy
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1800015574. Not yet recruiting as of 8 March 2022.

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ChiCTR1900020636 2019

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-38 years; tubal factor, male factor or unexplained infertility; first IVF/ICSI cycle; normal ovarian reserve tests within the past six months; normal serum hormone results
Interventions	**Arm 1:** follicular phase downregulation **Arm 2:** luteal phase downregulation
Outcomes	Live birth; clinical pregnancy; ongoing pregnancy; oocyte umbe ; preg ancy loss
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1900020636. Not yet ecruiting as of 14 September 2021.

ChiCTR2000032969 2020

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** non-obstructive azoospermia patients who planned to undergo micro testicular sperm extraction (TESE)-ICSI including fresh TESE sperm and frozen-thawed sperm; female younger than 43 years **Exclusion criteria:** donor gam te u age; repeated failed implantation; severe intrauterine adhesions; untreated hydrosalpinx ab orm l SFA
Interventions	**Arm 1:** early follicular phase l ng protocol **Arm 2:** antagonist regimen
Outcomes	Cumulative live birth
Notes	www.who.in tria ear h/Trial2.aspx?TrialID=ChiCTR2000032969. Not yet recruiting as of 8 March 2022.

ChiCTR2000034025 2020

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <35 years; low ovarian reserve (Poseidon 3 subgroup criteria, including AFC 5 or AMH <1.2ng/ml); fewer than 2 previous IVF cycles **Exclusion criteria:** >3 ovulation induction cycles; severe endometriosis; hydrosalpinx; endometrial adhesions; uterine malformation; chromosomal abnormalities
Interventions	**Arm 1:** long GnRH agonist **Arm 2:** short GnRH antagonist
Outcomes	Review outcomes not reported.
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000034025. Not yet recruiting as of 8 March 2022.

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ChiCTR2000034834 2020

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-35 years; AMH >1.1ng/l; fresh embryo transfer **Exclusion criteria:** decreased ovarian reserve function (standard FSH > 15IU/l, total bilateral AFC < 5, AMH # 1.1ng/l); PCOS; untreated hydrosalpinx; untreated endometrial polyps; moderate to severe intrauterine adhesions; endometriosis, adenomyosis, uterine fibroids (except subserosal fibroids); number of spontaneous abortions ≥2 times or embryo transfer failure ≥2 times; abnormal thyroid function, immune abnormality, insulin resistance is not adjusted to normal levels; other medical and surgical diseases not suitable for pregnancy or affecting p egnancy; chromosomal abnormalities in either partner
Interventions	**Arm 1:** "antagonist halved" **Arm 2:** "routine medication"
Outcomes	Clinical pregnancy; multiple birth; early misc rriage; ong ing pregnancy
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=Ch CTR2000034834. Not yet recruiting as of 8 March 2022.

ChiCTR2000036593 2020

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 25-35 years; baseline FSH <10 IU/l; total AFC >15 by transvaginal ultrasound; >20 follicles with d amete > 12-14 mm during COS; no uterine and ovarian lesions; bilateral ovaries; tubal or male infert ity; first cycle of IVF treatment; 18≤ BMI ≤28 kg/m^2 **Exclusion criteria:** e dometriosis; uterine malformation or endometrial organic lesions; bilateral hydrosalpinx history of recurrent miscarriage; other internal and external diseases affecting endocrine profil
Interventions	**Arm 1:** p ogest rone primed ovarian stimulation A m **2:** GnRH antagonist
Outcomes	Clinical p gnancy
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000036593. Not yet recruiting as of 8 March 2022.

ChiCTR200003681 2020

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-40 years; PCOS; freeze-all embryos strategy **Exclusion criteria:** previous history of failed IVF (>2 cycles); past history of empty follicles; endometriosis grade III or above; systemic diseases (such as severe liver and kidney diseases); hormonal therapy used within 3 months before study enrolment
Interventions	**Arm 1:** late follicular phase ovarian stimulation

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ChiCTR2000036810 2020 *(Continued)*

	Arm 2: GnRH antagonist regimen
Outcomes	Oocyte number; clinical pregnancy; miscarriage
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000036810. Not yet recruiting as of 14 September 2021.

ChiCTR-IIR-16007770 2016

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=C iCTR-IIR 16007770. Authors contacted (kuangyan-p@126.com) on 15 September 2021. Reply awaited. Access to trial registration not available on 8 March 2022.

ChiCTR-INR-16009541 2017

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 25 42 ye rs; BMI 18-25kg/m^2; normal ovarian reserve (basal FSH <10 IU/l, AFC >5, AMH level > 1.0 ng/ml); ≥2 IVF failures using traditional protocols (long protocol, ultra-long protocol and short protoc l a d GnRH antagonist protocol)
Interventions	**Arm 1:** ultra-long protoc l **Arm 2:** progestin-primed ovarian stimulation
Outcomes	Oocyte number; cl nical pregnancy; miscarriage; ectopic pregnancy; live birth
Notes	www ho.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-INR-16009541. Access to trial registration not available n 8 March 2022.

ChiCTR-INR-17013376 202

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** tubal disease; normal SFA
Interventions	**Arm 1:** GnRH antagonist and GnRH agonist **Arm 2:** ultras-short GnRH analogue (unclear if agonist or antagonist)
Outcomes	Clinical pregnancy

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ChiCTR-INR-17013376 2020 *(Continued)*

Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-INR-17013376. Access to trial registration not available on 8 March 2022.

ChiCTR-IOR-15006633 2015

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-40 years; PCOS
Interventions	**Arm 1:** Utrogestan® **Arm 2:** GnRH antagonist
Outcomes	Oocyte number; OHSS
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID ChiCTR-IOR 15006633. Access to trial registration not available on 8 March 2022.

ChiCTR-IOR-16009348 2016

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-40 years no mal menstrual cycles (23-35 days); tubal or male factors; basal FSH <10 IU/l; AFC 4
Interventions	**Arm 1:** mid-late follicular stimula ion (hMG) **Arm 2:** luteal phase stim lat n (letrozole and hMG)
Outcomes	Oocyte number
Notes	www.who.i /trialsearch/Trial2.aspx?TrialID=ChiCTR-IOR-16009348. Access to trial registration not availabl on 8 March 2022.

ChiCTR-IOR-17013082 2017

Methods	Randomised controlled trial
Participants	**clusion criteria:** aged 24-37 years; PCOS according to the Rotterdam criteria; first IVF-ET cycle **Exclusion criteria:** hydrosalpinx; history of uterine organic lesions (e.g., intrauterine tuberculosis, intrauterine adhesions) and uterine malformations
Interventions	**Arm 1:** ultra-long GnRH agonist **Arm 2:** daily GnRH agonist
Outcomes	Clinical pregnancy
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-IOR-17013082. Not yet recruiting as of 8 March 2022.

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ChiCTR-IOR-17013464 2017

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** low-responding women younger than 43 years old (defined by the Bologna criteria) **Exclusion criteria:** congenital uterine malformation; uncovered endometrium diseases; bilateral hydrosalpinges; severe disease including diabetes, hypertension and thyroid diseases
Interventions	**Arm 1:** low-dose gonadotrophin protocol with GnRH antagonist **Arm 2:** clomifene citrate plus gonadotrophin
Outcomes	Cancellation; clinical pregnancy; oocyte number; ongoing pregnancy; live birth
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR IOR-17013464. Not yet recruiting as of 8 March 2022.

ChiCTR-OPR-15006204 2015

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <38 years; basel e FSH <10 IU/l; AFC >5
Interventions	**Arm 1:** rFSH plus HP-hMG **Arm 2:** HP-hMG
Outcomes	Review outcomes not repor ed
Notes	www.who.int/tr alsea ch/Trial2.aspx?TrialID=ChiCTR-OPR-15006204. Access to trial registration not available on 8 Marc 202 .

Choi 2005a

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Full text not found

Choi 2012

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 28-41 years; PCOS

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Choi 2012 *(Continued)*

Interventions	**Arm 1:** IVM/IVF with FSH and hCG priming **Arm 2:** GnRH agonist long protocol **Arm 3:** GnRH antagonist multi-dose flexible protocol
Outcomes	Clinical pregnancy; live birth; miscarriage
Notes	Authors emailed (novak21c@yahoo.co.kr) on 26 February 2021 as the manuscript contains no details of gonadotrophins used for COS. Reply awaited.

CTRI/2012/05/002656 2012

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** regular menstrual cycles o 24-35 day ; normal baseline FSH and LH during the early follicular phase, AFC >5, normal functio al ovaries a d uterus; infertility due to any of the following factors: tubal factor, endometriosis (stage 1 or 2) male factor or unexplained factor **Exclusion criteria:** uterine fibroids; subjects with primary ovarian failure, uncontrollable hyperthyroidism or secondary adrenal insufficiency BMI ≥30 kg/m^2; subjects with previous history of OHSS in previous IVF cycles; more than 3 previously consecutive unsuccessful IVF cycles; any significant systemic disease, endocrine or metabo c abn rmalities; tumours of the ovary, breast, uterus, hypothalamus or pituitary gland; ovar n cysts or enlarged ovaries, not related to PCOS; intracranial bleeding; organic intracranial lesion such as pituitary tumour; HIV or syphilis positive subjects; history of alcohol or drug addicti n; s bjects smoking more than 5 cigarettes per day; history of hypersensitivity to hMG or other h rmaceutical excipients of this drug; positive serum pregnancy test; undiagnosed vaginal bleeding; participation in any other clinical trial within 3 months of registering in this study
Interventions	**Arm 1:** hMG (downregula ion unstated) **Arm 2:** hMG (downregulation unstated)
Outcomes	Oocyte number; clinical pregnancy rate; OHSS
Notes	Au hors c ntacted (mita.nandy@lglsi.com) on 16 September 2021. Response awaited.

CTRI/2016/10/007367 2016

Methods	Ra domised controlled trial
Participants	**nclusion criteria:** age 22-38 years of age with regular menstrual cycle of 24-35 days; female patients undergoing COS for ART; BMI 18-30 kg/m^2; transvaginal ultrasound documenting the presence of both ovaries without abnormalities and normal uterine adnexa; clinically acceptable ranges of basal FSH, LH, oestradiol at the time of enrolment; AFC 8-25 (sum of both ovaries); willing to comply with all the study requirements and procedures; normal or clinically insignificant haematology, serum chemistry and urinalysis parameters during screening **Exclusion criteria:** history of allergy or hypersensitivity reactions to FSH or any other ingredients of the formulation; use of any FSH preparation or clomifene citrate within 60 days of randomisation; history of ≥2 succeeding ART retrieval cycles (which includes fresh and frozen embryo transfers before the study cycle without clinical pregnancy; presence of polycystic ovaries; previous history of severe OHSS; presence of severe endometriosis (ASRM stage 3 or stage 4) and hydrosalpinx; presence or history of thrombophlebitis or thromboembolic disorders; history of extrauterine preg-

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CTRI/2016/10/007367 2016 *(Continued)*

	nancy in the previous 3 months; history of poor response to gonadotropin treatment (defined <5 oocytes retrieved in a previous attempt); subjects with clinically significant unstable medical disorders, life-threatening disease, or current malignancies; positive cervical smear at screening; combination or hormonal implants ≤6 months prior to screening; positive pregnancy test at screening
Interventions	**Arm 1:** rFSH (downregulation unstated) **Arm 2:** rFSH (downregulation unstated)
Outcomes	Oocyte number
Notes	Authors contacted (ddomadia@claintha.in) on 16 September 2021. Response awaited.

CTRI/2017/11/010317 2017

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-39 years; regular m nstrual cy les; normal baseline FSH and oestradiol; AFC 10-25; BMI >18.5 to <30 kg/m^2 **Exclusion criteria:** history of >2 successive ART cycles without clinical pregnancy; history of any endocrine abnormality; history of OHSS; documented PCOS; ovarian abnormality; severe endometriosis; submucosal fibroid; history of auterine pregnancy in past 3 months; history of miscarriages; low response to gonadotrophin treatment; positive HIV, hepatitis B or C; known case of allergy to r-hmg or its excipients; history of other comorbidity preventing participation in trial under investigators discretion history of addiction
Interventions	**Arm 1:** rhMG (downregulat n uns ted) **Arm 2:** HP-hMG (downreg lation unstated)
Outcomes	Oocyte number; ongoing pregnancy
Notes	Authors contact d (drkaminirao@milann.co.in) on 8 March 2022. Response awaited.

Daya 2003

Methods	Randomis d controlled trial
Participants	Women undergoing COS with follitropin alfa or beta
Interventions	**rm 1:** follitropin alfa (downregulation unclear) **Arm 2:** follitropin beta (downregulation unclear)
Outcomes	Review outcomes not reported
Notes	Insufficient data to extract from the abstract. Up-to-date author contact details not found.

Depalo 2003

Methods	"Prospective study", unclear if randomised

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Depalo 2003 *(Continued)*

Participants	Women undergoing COS for ART
Interventions	**Arm 1:** short GnRH antagonist plus rFSH **Arm 2:** long GnRH agonist plus rFSH
Outcomes	Oocyte number; cleavage embryo number
Notes	Unclear if this study was a randomised controlled trial. No contact details for the authors.

Devesa 2008

Methods	Randomised controlled trial
Participants	Women with low ovarian response
Interventions	**Arm 1a:** long GnRH agonist plus rFSH (n =?) **Arm 1b:** long GnRH agonist plus rFSH and hMG (n =?) **Arm 2a:** short GnRH agonist plus rFSH (n =) **Arm 2b:** short GnRH agonist plus rFSH and h (n =?) **Arm 3a:** short GnRH antagonist plus rFSH (=?) **Arm 3b:** short GnRH antagon t plus rFSH and hMG (n =?)
Outcomes	Cancellation; oocyte number; linical pregnancy
Notes	Insufficient informati in th abstract to extract data pertaining to each arm. Up-to-date author contact details not found.

Dirnfeld 1999a

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Full text not found

Domitrz 2003

Methods	Unstated
Participants	**Inclusion criteria:** age <35 years; tubal factor infertility
Interventions	**Arm 1:** short GnRH agonist flare plus FSH (formulation unstated)

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Domitrz 2003 *(Continued)*

	Arm 2: short GnRH antagonist plus FSH (formulation unstated)
Outcomes	Clinical pregnancy
Notes	Unclear whether the study was randomised. No contact details for authors.

Eftekhar 2013

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** history of ≥1 failed IVF cycles with <4 retrie ed oocytes no age limits **Exclusion criteria:** BMI >30 kg/m^2; endocrine or metabo ic disorders; endometriosis; severe male factor (azoospermia)
Interventions	**Arm 1:** agonist flare plus hMG (n = 60) **Arm 2:** agonist flare plus hMG plus antagonist (n = 60)
Outcomes	Clinical pregnancy; oocyte number
Notes	Awaiting additional information from he trial authors.

Eftekhar 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** ag 20-45 years; ≥1 previous failed ART cycles in which <4 oocytes were retrieved and serum oestradiol levels ≤500 pg/ml on the day of hCG administration **Exclusion crite ia:** BMI >30 kg/m^2; endocrine or metabolic disorders; history of ovarian surgery; severe endometri sis; azoospermia in the male partner; FSH >15 mIU/ml
Interventions	**Arm 1:** short ant gonist plus clomifene citrate plus hMG (n = 92) **Arm 2:** short antagonist plus letrozole plus hMG (n = 92)
Outcomes	Clinical pregnancy; miscarriage; oocyte number
Notes	Awaiting additional information from the trial authors.

Eftekhar 2019

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** PCOS (Rotterdam criteria) **Exclusion criteria:** intrauterine anomalies (fibroids, polyps, adhesions); severe endometriosis; systemic conditions; azoospermia
Interventions	**Arm 1:** progestogen plus rFSH (n = 60)

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Eftekhar 2019 *(Continued)*

	Arm 2: short antagonist plus rFSH (n = 60)
Outcomes	OHSS; clinical pregnancy; miscarriage; cancellation; oocyte number
Notes	Awaiting additional information from the trial authors.

Eftekhar 2020

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-40 years; normal ovarian reserve (A C >7, AMH 1-3.5 ng/ml) **Exclusion criteria:** endocrine abnormalities; intrauterin disorders; severe endometriosis; male azoospermia
Interventions	**Arm 1:** short antagonist plus letrozole plus rF H (n = 50) **Arm 2:** short antagonist plus rFSH (n = 50)
Outcomes	OHSS; clinical pregnancy
Notes	Awaiting additional information from the trial authors.

Elnashar 2016

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** n rmal-r sponding women undergoing COS for ART; age 20-35 years; BMI 18-29 kg/m^2; unexplained infertility; AFC >5 per ovary; AMH >1 ng/dl
Interventions	**Arm 1:** short Gn H antagonist plus letrozole and FSH (formulation unstated) **Arm 2:** long nRH agonist plus FSH
Outcomes	Oocyte n mber
Notes	Insuffic nt data from the abstract. No contact details for the authors. Trial registration website (NCT02429999) states that recruitment status is unknown as of 15 July 2016.

EUCTR2010-022032 37-IT 011

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** low-responding women undergoing COS for ART; age 35-43 years; regular menstrual cycles 26-33 days; tubal or male factor infertility; no COS within the previous 3 months; baseline FSH >10 and <15 mIU/ml; previous low response **Exclusion criteria:** hypogonadotrophic hypogonadism; participation in another clinical trial within the past 30 days; known hypersensitivity to the trial treatment, or the comparator drug; legal incapacity or limited legal capacity; any clinically important systemic disease (e.g., insulin-dependent diabetes mellitus, epilepsy, serious migraine, intermittent purpura, hepatic, renal or cardiovascu-

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EUCTR2010-022032-37-IT 2011 *(Continued)*

	lar disease, serious corticoid-dependent asthma) constituting a contraindication to gonadotrophin use
Interventions	**Arm 1:** rFSH (downregulation unstated) **Arm 2:** rFSH and rLH (downregulation unstated)
Outcomes	Oocyte number
Notes	Trial registration entry states it is concluded but no results or contact details found online.

EUCTR2012-004824-39-GB 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** women aged 23-39 years; MI 19-30 g/m^2; serum FSH 10-14.99 mIU/l; low AMH (3.08-21.97 pmol/l)
Interventions	**Arm 1:** short GnRH agonist protocol **Arm 2:** short GnRH antagonist protocol
Outcomes	Live birth
Notes	www.who.int/trialsearch/Trial2 aspx?TrialID=EUCTR2012-004824-39-GB. Only a total of 4 patients recruited for this trial.

EUCTR2014-005099-27-ES 2015

Methods	Randomised co troll d trial
Participants	**Inclusion cr teria:** female age 18-38 years (inclusive); BMI <30 kg/m^2; diagnosis of PCOS (according to Rotterdam criteria); basal FSH levels ≤10 IU/l; presence of both ovaries and uterus able to sup- po emb yo imp ntation and pregnancy; absence of pregnancy before starting ovarian stimula- t on **Exclus n criteria:** severe male factor not allowing ART with ejaculated sample; low ovarian re- serve; important endocrine-metabolic systemic diseases affecting pituitary, thyroid, adrenals, pan- creas, liver or kidney; HIV seropositivity; frozen embryos from previous ART cycles; undiagnosed vaginal haemorrhage; poor response in previous cycles of FIV with standard stimulation protocols; pr gnancy, lactation or contraindication to pregnancy; malformations of the sexual organs incom- patible with pregnancy; history of allergy to gonadotrophin preparations or its excipients; alcohol, drugs or psychotropic addiction; concurrent participation in another study; previous history of se- vere hyperstimulation syndrome; concomitant medication that may interfere with the study med- ication: different hormonal treatments used in the study, other thyroid hormones, antipsychotics, anxiolytics, hypnotics, sedatives, chronic treatment with inhibitors of prostaglandin
Interventions	**Arm 1:** short GnRH antagonist plus uFSH **Arm 2:** short GnRH antagonist plus hMG
Outcomes	Oocyte number; live birth; miscarriage; cancellation

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EUCTR2014-005099-27-ES 2015 *(Continued)*

Notes	Ended prematurely. Emailed to obtain trial results. Initial response from cdelgadoe@santpau.cat redirected to jespinos@santpau.cat, emailed on 6 April 2021. Response awaited.

EUCTR2015-005660-42-ES 2016

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-38 years; BMI <30 kg/m^2; PCOS (Rotterdam criteria); FSH ≤10 IU/l; presence of both ovaries and uterus able to support embryo implantation nd pregnancy; absence of pregnancy before starting ovarian stimulation **Exclusion criteria:** severe male factor not allowing for IVF/ICSI; low ovarian reserve; endocrine-metabolic systemic conditions affecting the pituitary, yroid, adrenal glands, pancreas, liver or kidneys; HIV carrier; previous low response
Interventions	**Arm 1:** GnRH antagonist plus HP-hMG **Arm 2:** GnRH antagonist plus HP-uFSH
Outcomes	Oocyte number; live birth; miscarriage; cancellation
Notes	Ended prematurely. Emailed epenag@ ntpau.cat on 31 March 2021, reply awaited.

EUCTR2018-002000-13-BE 2018

Methods	Randomised controlled rial
Participants	**Inclusion criteria:** age 18 t < 38 years; not more than three consecutive unsuccessful IVF/ICSI cycles since the last going pregnancy (whether fresh and/or several frozen ET resulted from these attempts); BMI 29 kg/m^2; regular normo-ovulatory menstrual cycles (26–35 days); basal FSH <10 IU/l, basal E2 <60 pg/ml nd basal progesterone <1.5 ng/ml; normal cycle day-3 basal serum hormone levels to be measured on cycle day 2 or 3 of the treatment cycle; normal ultrasound scan (pres e of b th ovaries without evidence of abnormality within 6 months); AFC >7 and < 20; no pill within the 3 m nths before treatment **Exc usi n criteria:** PCOS according to the Rotterdam classification (2004); oocyte donor; low ovarian resp nse (development of <4 follicles in previous IVF/ICSI or cancelled cycles); endometriosis ≥ grade 3; contraindications to the use of gonadotrophins; abnormal vaginal bleeding of unknown cause; history of OHSS or a previous ovarian stimulation cycle with more than 30 follicles of 11 mm or higher; history of recurrent miscarriage (three or more consecutive miscarriages)
Interventions	**rm 1:** short GnRH antagonist plus corifollitropin alfa **Arm 2:** short GnRH antagonist plus rFSH and corifollitropin alfa
Outcomes	Oocyte number; clinical pregnancy; ongoing pregnancy; miscarriage
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018-002000-13-BE. Trial status "ongoing" as of 9 March 2022.

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Evangelio 2011

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Full text not found

Ferraretti 1999

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <38 years; previous low ovarian r sponse
Interventions	Various combinations of rFSH and uFSH, with r without pituitary downregulation
Outcomes	Cancellation; oocyte number; miscarriage
Notes	Insufficient data from the abstract to ex ract. Author contact details not found.

Ferraretti 2014

Methods	Randomised controlled rial
Participants	**Inclusion criteria:** age 38 y ars; previous low response; normo-ovulatory cycles, normal ovaries and uterus; normal karyotype
Interventions	**Arm 1:** agonist or antagonist protocol plus rFSH **Arm 2:** agon t or antagonist protocol plus rFSH and rLH
Outcomes	C ncellat on; ocyte number; clinical pregnancy; live birth; miscarriage
Notes	Addition l information sought from annapia.ferraretti@sismer.it, emailed on 16 September 2021. Reply awaited.

Ferrero 2010

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** previous moderate or severe OHSS using a long GnRH agonist protocol **Exclusion criteria:** unstated
Interventions	**Arm 1:** short GnRH antagonist plus rFSH (n = ?) **Arm 2:** long GnRH agonist plus rFSH (n = ?)
Outcomes	Cancellation; oocyte number; clinical pregnancy; live birth

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Ferrero 2010 *(Continued)*

Notes	Insufficient allocation details (no total number of women per arm) to include. No author contact details available.

Fiedler 2001

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** normo-ovulatory cycles
Interventions	**Arm 1:** short GnRH antagonist plus clomifene/FSH/hMG **Arm 2:** clomifene/rFSH/hMG (no pituitary suppression)
Outcomes	Ongoing pregnancy or live birth; OHSS; multiple pregnan y
Notes	Insufficient data from the abstract to add - FSH formulat n unknown. No author contact details found.

Filicori 1999

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** unexplained or mal -related infertility; regular menstrual cycles of 26 to 34-day duration; BMI 20-25 kg/m^2; normal ovaries and uterus; tubal patency demonstrated by hysterosalpingogram and/or laparos opy; normal plasma and urinary chemistry and haematological values; thyroid and reprodu tive ho mones within the normal range; no hormone therapy for at least 3 months prior to the study
Interventions	**Arm 1:** long GnRH ag nist plus uFSH **Arm 2:** long GnRH agoni t plus uFSH/uhCG
Outcomes	Revi w utcomes not reported
Notes	A ditional information sought from authors on 16 September 2021 (filicori@med.unibo.it). Reply awai .

Filicori 2005

Methods	andomised controlled trial
Participants	**Inclusion criteria:** age 29-39 years; regular menstrual cycles (26-32 days); BMI 20-25 kg/m^2; normal uterus and ovaries on ultrasound; normal baseline biochemical and endocrine levels; reproductive hormones within the normal range for early/midfollicular phase of the cycle; no history or signs of endometriosis; moderate or severe oligospermia **Exclusion criteria:** >2 previous IVF/ICSI cycles; previous low response to gonadotrophin stimulation; hormonal therapy within the three months preceding the study
Interventions	**Arm 1:** Long agonist plus hMG/rFSH (n = ?)

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Filicori 2005 *(Continued)*

	Arm 2: Long agonist plus hMG/rFSH/uhCG (n = ?)
Outcomes	Review outcomes not reported
Notes	Unclear how many women were assigned to each arm. Additional information sought from authors on 16 September 2021 (filicori@med.unibo.it). Reply awaited.

Fillicori 1995

Methods	Unstated
Participants	**Inclusion criteria:** eumenorrhoeic women
Interventions	**Arm 1:** uFSH only **Arm 2:** short GnRH agonist flare plus uFSH **Arm 3:** long GnRH agonist plus uFSH **Arm 4:** long GnRH agonist plus hMG
Outcomes	Review outcomes not reported
Notes	Unclear whether RCT. Insufficient data from the abstract to extract. Author contact details not found.

Frattarelli 2007

Methods	Randomised controlled tri l
Participants	**Inclusion crite a:** age < 0 years; BMI <33 kg/m^2; day 3 FSH <10 IU/l; day 3 oestradiol <80 pg/ml; AFC >10; reg ar o ulat ry cycles **Excl si n crit ria:** unstated
Interventions	**A m 1:** s ort GnRH antagonist plus rFSH only (n = ?) **Arm 2:** s ort GnRH antagonist plus rFSH and low dose hCG (n = ?) **Arm 3:** short GnRH antagonist plus rFSH and hMG (n = ?)
Outcomes	Oocyte number; embryo number
Notes	Allocation numbers unstated, therefore awaiting classification

Friedler 2003

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <40 years; male or tubal infertility
Interventions	**Arm 1:** short GnRH antagonist

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Friedler 2003 *(Continued)*

	Arm 2: GnRH agonist (duration unstated)
Outcomes	Clinical pregnancy
Notes	Unclear which gonadotrophins were used in this study. No contact details found for the authors.

Fries 1990

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** women undergoing COS for ART
Interventions	**Arm 1:** "standard" GnRH agonist plus uFSH **Arm 2:** "standard" GnRH agonist plus hMG
Outcomes	Oocyte number
Notes	Insufficient data from the abstract to extract. Autho contact details not found.

Galal 2012

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** PCOS
Interventions	**Arm 1:** hMG (pituitary suppression unstated) **Arm 2:** letrozole and hMG (pituitary suppression unstated)
Outcomes	Oocyte number; clinical pregnancy
Notes	Insuffi ient information in the abstract. No contact details for the authors.

Geber 2001

Methods	Randomised controlled trial
Participants	All women undergoing IVF treatment
Interventions	**Arm 1:** long GnRH agonist (from midluteal phase of previous cycle), gonadotrophin unstated **Arm 2:** GnRH agonist (from follicular phase), however unclear whether agonist flare or long protocol, gonadotrophin unstated
Outcomes	Oocyte number
Notes	Insufficient data from the abstract to include. No contact details for the authors.

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Ghahghaei Nezamabadi 2013

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** normal-responding women
Interventions	**Arm 1:** GnRH agonist (unclear whether long or flare, gonadotrophin unstated) **Arm 2:** GnRH antagonist (gonadotrophin unstated)
Outcomes	Oocyte number; clinical pregnancy; ongoing pregnancy
Notes	No details of gonadotrophins used, therefore unable to extract data.

Ghosh 1999

Methods	Unclear
Participants	**Inclusion criteria:** age <37 years; normal cyc length; ba eline FSH <12 mIU/l, no other endocrine abnormality; baseline pelvic ultrasound showing no ut rine tumour or ovarian cyst; male partner normal SFA; no previous OHSS **Exclusion criteria:** PCO
Interventions	**Arm 1:** long GnRH agonist plus rFSH **Arm 2:** long GnRH agonist plus uFSH
Outcomes	Oocyte number; OHSS
Notes	Unclear if RCT. No contact details ound for the authors.

Ghosh 2010

Methods	Rand ised c ntrolled trial
Participants	**Inclusio criteria:** first ART cycle
Interventions	**Arm 1:** sh rt GnRH antagonist plus clomifene citrate and rFSH **Arm 2:** long GnRH agonist plus rFSH
Outcomes	Oocyte number
Notes	Insufficient information from the abstract (unclear how many women were allocated to each group). Author contact details not found.

Grochowski 1999

Methods	Unstated
Participants	**Inclusion criteria:** age <36 years; regular menstrual cycles (25-35 days)
Interventions	**Arm 1:** clomifene citrate plus hMG (n = 164 cycles)

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Grochowski 1999 *(Continued)*

	Arm 2: long GnRH agonist plus hMG (n = 160 cycles)
Outcomes	Oocyte number; multiple pregnancy; severe OHSS
Notes	Unclear if randomised. No contact details for authors.

Grow 1992

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** at least one of the following: age ≥39 years; previous very low response; or elevated baseline serum FSH (≥15 mIU/ml) with or without a high bas line se um oestradiol (>50 pg/ml)
Interventions	**Arm 1:** FSH (formulation unstated) **Arm 2:** short GnRH agonist flare plus FSH (fo mulation un tated)
Outcomes	Cancellation; oocyte number; clinical pregnancy; arriage
Notes	Formulation of type of gonadotrophin used (FSH) unclear, therefore unable to extract data. Author contact details not found.

Heijnen 2007

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** tub l ma e or unexplained subfertility; age <38 years; menstrual cycle 25-35 days; BMI 18-28 kg/m^2
Interventions	**Arm 1:** short Gn H antagonist (gonadotrophin formulation unstated) (n = 205) **Arm 2:** long nRH agonist (gonadotrophin formulation unstated) (n = 199)
Outcomes	L e birth OHSS; ongoing pregnancy; cancellation; oocyte number; number of embryos cryopreserv d
Notes	No details of stimulation protocols. Authors emailed on 7 April 2021 (bfauser2@umcutrecht.nl; b.c.fauser@umcutrecht.nl), response awaited.

Hines 2002

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** first IVF cycle; age ≤39 years; no previous low response
Interventions	**Arm 1:** long GnRH agonist plus rFSH **Arm 2:** long GnRH agonist plus FSH/LH (unclear formulation)
Outcomes	Oocyte number

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Hines 2002 *(Continued)*

Notes	Insufficient data in the abstract (unclear FSH/LH formulation), therefore awaiting classification. No contact details for the authors.

Hiroi 1993

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Full text not found

Hussain 2019

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age ≤35 years; normal ovulatory menstrual cycles; tubal or male factor infertility **Exclusion criteria:** age >35 year ; PCOS; endometriosis; unexplained or severe male factor infertility
Interventions	**Arm 1:** rFSH and hMG (down egulation achieved either with GnRH antagonist or agonist, however numbers not specified) **Arm 2:** hMG (downregul tion achieved either with GnRH antagonist or agonist, however numbers not specified)
Outcomes	Oocyte number; l nical pregnancy rate
Notes	Uncl ar how d wnregulation was undertaken. Authors contacted on 16 September 2021 (doc- to 89mu ah@yahoo.com), response awaited.

Inza 2004

Methods	Ra domised controlled trial
Participants	**nclusion criteria:** age <40 years; baseline serum FSH ≤12 IU/ml
Interventions	**Arm 1:** long GnRH agonist, gonadotrophin formulation unstated (n = 22) **Arm 2:** short GnRH antagonist, gonadotrophin formulation unstated (n = 23)
Outcomes	Oocyte number
Notes	Insufficient data in the abstract due to lack of information on gonadotrophin formulation used. Author contact details not found.

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IRCT138901193636N 2010

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-35 years; PCOS; normal karyotype **Exclusion criteria:** other causes of anovulation (hypo or hyper gonadotropic hypogonadism, Cushing syndrome, hyperprolactinaemia), previous low response to COS
Interventions	**Arm 1:** uFSH (downregulation unstated) **Arm 2:** rFSH (downregulation unstated)
Outcomes	Clinical pregnancy; oocyte number; ongoing pregnancy; misc rriage
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT138901193 36N1. Authors contacted on 15 September 2021 (sheikhhasani86@razi.tums.ac.ir). Reply awaited

IRCT20110509006420N 2018

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** women undergoing COS for ART **Exclusion criteria:** history of endocrin di orders; intrauterine abnormality (uterine polyp, submucosal fibroids and intrauterine adhesions); azoospermia in male partner; severe endometriosis
Interventions	**Arm 1:** short GnRH antagonist plus rFSH **Arm 2:** short GnRH antag nist p us letrozole and rFSH
Outcomes	Clinical pregnancy; miscar a e
Notes	www.who.int/t alsearch/Trial2.aspx?TrialID=IRCT20110509006420N19. Authors contacted on 16 September 2 21 ftekhar@ssu.ac.ir). Reply awaited.

IRCT201106026689N1 2014

Methods	Randomised controlled trial
Participants	**nclusion criteria:** age 20-43 years; predicted low response **xclusion criteria:** severe male infertility; severe endometriosis; uterine fibroids (≥4 cm)
Interventions	**Arm 1:** long GnRH agonist plus rFSH replaced by hMG **Arm 2:** short GnRH agonist flare plus rFSH and hMG
Outcomes	Oocyte number; clinical pregnancy; cancellation
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201106026689N1. Authors contacted on 15 September 2021 (hoseinimosa@sina.tums.ac.ir). Reply awaited.

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IRCT201107286420N5 2011

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <38 years; regular menstrual cycle (25-35 days); BMI <30 kg/m^2; normal uterus and ovaries on transvaginal ultrasound; serum FSH <10 IU/l **Exclusion criteria:** severe endometriosis; PCOS; previous pelvic surgery; azoospermia; >2 previous failed IVF/ICSI cycles
Interventions	**Arm 1:** long GnRH agonist plus hMG **Arm 2:** long GnRH agonist plus hMG replaced by hCG
Outcomes	Clinical pregnancy
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2011072864 0N5. Authors contacted on 15 September 2021 (eftekhar@ssu.ac.ir). Reply awaited.

IRCT20110731007165N 2019

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-44 years; previo s l w response; AFC <5-7; AMH <0.5-1.1 ng/ml **Exclusion criteria:** PCOS; amenorrhoe ; u erine congenital and acquired anomalies; >3 previous IVF failed cycles
Interventions	**Arm 1:** short GnRH antagonist p us rFSH **Arm 2:** long GnRH agonis plus rFSH
Outcomes	Oocyte number; clinical preg ancy; ongoing pregnancy
Notes	www.who.int/t als arch Trial2.aspx?TrialID=IRCT20110731007165N10. Authors contacted on 16 September 2 21 (ashani_ladan@tums.ac.ir). Reply awaited.

IRCT201109136626N 2011

Methods	Randomised controlled trial
Participants	**clusion criteria:** age >35 years **xclusion criteria:** endocrine disease or hypertension; PCOS; endometriosis; previous ovarian urgery
Interventions	Interventions unclear in the trial registry entry
Outcomes	Clinical pregnancy; miscarriage; OHSS; oocyte number
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201109136626N3. Authors contacted on 15 September 2021 (dr-abdollahi@tbzmed.ac.ir). Reply awaited.

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IRCT201111058010N 2012

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-40 years
Interventions	**Arm 1:** long GnRH agonist plus rFSH **Arm 2:** short GnRH antagonist plus rFSH
Outcomes	Clinical pregnancy; OHSS
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201111058010N1. Authors contacted on 15 September 2021 (maryam.hedayat@umsha.ac.ir). Reply awaited

IRCT201202128977N 2012

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 36-42 years; baseline FSH 12 IU/l; BMI <32 kg/m^2; regular menstrual cycles (21-35 days); no COS within the past three months **Exclusion criteria:** previous low response; medical conditions affecting gonadotrophin pharmacokinetics; previous OHSS; PCOS; endometr si uterine fibroids; contraindication to pregnancy; ≥3 previous miscarriages
Interventions	Interventions (gonadotrophin orm lations) unclear in the trial registry entry
Outcomes	Oocyte number
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201202128977N1. Authors contacted on 15 September 2021 (marj gh emi@farzaninstitute.com). Reply awaited.

IRCT201205309910N 2012

Methods	Randomised controlled trial
Participants	**Inclus n criteria:** first ART cycle; age ≤35 years; serum FSH level ≤10 IU/l **Exclusion criteria:** previous ART cycle; hyperprolactinaemia, thyroid dysfunction, uterine abnormality, severe endometriosis and secondary infertility
Interventions	**Arm 1:** long GnRH agonist plus FSH (formulation unstated) **Arm 2:** short GnRH antagonist plus FSH (formulation unstated)
Outcomes	OHSS; oocyte number
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201205309910N1. Authors contacted on 15 September 2021 (setare_n99@yahoo.com). Reply awaited.

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IRCT201211197165N 2012

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-39 years; BMI 20-25 kg/m^2; normal uterus; two functioning ovaries; day 3 FSH < 10 IU/l; serum oestradiol <60 pg/ml **Exclusion criteria:** >2 previous unsuccessful IVF/ICSI attempts; low ovarian response in previous ART cycle
Interventions	**Arm 1:** short GnRH antagonist plus rFSH **Arm 2:** short GnRH antagonist plus rFSH and low-dose hCG
Outcomes	Review outcomes not reported.
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20121 197165N2. Authors contacted on 15 September 2021 (kashani_ladan@tums.ac.ir). Reply awa ted.

IRCT201302271760N 2013

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age >37 years; low ova ian response; previous <5 oocytes recovered **Exclusion criteria:** chronic diseases; e do rine diseases; submucous polyps; uterine fibroids; uterine septum
Interventions	**Arm 1:** long GnRH agonist plus MG **Arm 2:** short GnRH antag nist p s hMG (?added hCG) - details unclear
Outcomes	Oocyte number; cancellatio ; OHSS
Notes	www.who.int/t als arch Trial2.aspx?TrialID=IRCT201302271760N21. Authors contacted on 15 September 2 21 (ahra@mubabol.ac.ir). Reply awaited.

IRCT201402041760N 2014

Methods	Randomised controlled trial
Participants	**clusion criteria:** age ≤35 years; serum FSH <12 mIU/ml; PCOS (Rotterdam criteria) **xclusion criteria:** >2 previous miscarriages; uterine anomalies; ovarian cysts
Interventions	**Arm 1:** long GnRH agonist plus hMG or rFSH **Arm 2:** short GnRh antagonist plus rFSH
Outcomes	Review outcomes not reported
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201402041760N30. Authors contacted on 16 September 2021 (zahra@mubabol.ac.ir). Reply awaited.

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IRCT2014030516858N 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-35 years; regular ovulatory menstrual cycles (26-35 days); >5 million sperm in SFA; BMI 18-30 kg/m^2; first IVF attempt **Exclusion criteria:** established systemic disease; ovary and uterine anomalies; recurrent miscarriage
Interventions	**Arm 1:** long GnRH agonist plus rFSH **Arm 2:** clomifene citrate and rFSH (downregulation unstated)
Outcomes	Clinical pregnancy; OHSS; multiple pregnancy; oocyte numb r; number of embryos cryopreserved
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20140 0516 58N1. Authors contacted on 16 September 2021 (drspeyvandi@mazums.ac.ir). Reply awaited.

IRCT201404065181N 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** low-responding wome **Exclusion criteria:** smoking; ovarian cysts or surgery; intolerance to gonadotrophin preparations; endocrine abnormalities
Interventions	**Arm 1:** short GnRH antagonist p us rFSH **Arm 2:** short GnRH antag nist p s rFSH then replaced by hMG
Outcomes	Miscarriage
Notes	www.who.int/t als arch Trial2.aspx?TrialID=IRCT201404065181N13. Authors contacted on 16 September 2 21 (hrashidi@tums.ac.ir). Reply awaited.

IRCT2014101919578N 2015

Methods	Randomised controlled trial
Participants	**clusion criteria:** age >30 years; low ovarian response **xclusion criteria:** age >50 years; letrozole intolerance; endocrine dysfunction; previous OHSS; act ve systemic disease
Interventions	**Arm 1:** short antagonist plus rFSH and hMG **Arm 2:** short antagonist plus letrozole and rFSH and hMG
Outcomes	Oocyte number; clinical pregnancy; cancellation
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2014101919578N1. Authors contacted on 16 September 2021 (maeb@tums.ac.ir). Reply awaited.

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IRCT2016022326711N 2016

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** normal ovarian response; BMI >30 kg/m^2 **Exclusion criteria:** low ovarian response; high ovarian response; donor egg cycles; single ovary; endometriosis; severe male factor
Interventions	**Arm 1:** short GnRH antagonist plus rFSH **Arm 2:** long GnRH agonist plus rFSH
Outcomes	Clinical pregnancy
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20160 2326711N1. Authors contacted on 16 September 2021 (aghahoseini@sina.tums.ac.ir). Reply waited.

IRCT2016091722903N 2016

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-44 years; BM 18 30 kg/m^2; low ovarian response according to Bologna criteria; no treatment with clomifene citr te within the previous month; normal mesntrual cycles; normal serum prolactin; normal uterine c ity as demonstrated by hydrosalpingography **Exclusion criteria:** age <18 and >44 ye rs; hypothalamic or pituitary tumour; endocrine disease; severe endometriosis
Interventions	**Arm 1:** short GnRH agonis flare p us rFSH **Arm 2:** short GnRH antagon plus rFSH
Outcomes	Oocyte number cancella ion
Notes	www.who.in /trialsearch/Trial2.aspx?TrialID=IRCT2016091722903N2. Authors contacted on 16 Sep emb r 2021 (sh-hoseini@razi.tums.ac.ir). Reply awaited.

IRCT201701291952N 2017

Methods	andomised controlled trial
Participants	**clusion criteria:** low ovarian response or reserve **Exclusion criteria:** other causes of infertility
Interventions	Interventions not fully described in trial registry entry
Outcomes	Clinical pregnancy
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201701291952N8. Authors contacted on 16 September 2021 (hosp_arash@tums.ac.ir). Reply awaited.

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IRCT20191205045621N 2020

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <42 years; regular menstrual cycles; AFC 7-24; normal TSH and prolactin levels **Exclusion criteria:** endometriosis grade 3 or higher; PCOS; ovarian cyst; contraindication to COS; serum FSH >10 IU/l
Interventions	**Arm 1:** medroxyprogesterone plus hMG **Arm 2:** GnRH agonist (duration unstated) plus hMG
Outcomes	Oocyte number; clinical pregnancy
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20191205045621N2. Authors contacted on 16 September 2021 (jafarish@resident.mui.ac.ir). Reply awaited

IRCT20200601047630N 2020

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-35 years; normal SFA; BMI 18-30 kg/m^2; both ovaries present; both tubes patent **Exclusion criteria:** tubal factor; severe endometriosis; hypothalamic amenorrhoea; oligoasthenospermia; severe uterine anomalies
Interventions	**Arm 1:** medroxyprogesterone plus FSH with or without hMG **Arm 2:** short GnRH antagoni plus FSH with or without hMG
Outcomes	Oocyte quality; clinical pregnancy
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20200601047630N1. Authors contacted on 16 September 2021 (anajafian@sina.tums.ac.ir). Reply awaited.

ISRCTN84867406 2011

Methods	Randomised controlled trial
Participants	No details found
Interventions	No details found
Outcomes	No details found
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN84867406. Authors contacted on 16 September 2021 (raja_alkaraki@alamalhospital.com). Reply awaited.

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Jindal 2013

Methods	Randomised controlled trial
Participants	Women undergoing COS for ART
Interventions	**Arm 1:** long GnRH agonist plus FSH (formulation unstated) **Arm 2:** short GnRH antagonist plus clomifene
Outcomes	Oocyte number; clinical pregnancy
Notes	This was a conference abstract and there is no contact details for the uthors. Insufficient data to extract.

JPRN-UMIN000008760 2012

Methods	Unclear
Participants	**Inclusion:** low-responding women undergoing OS for ART
Interventions	**Arm 1:** short GnRH antagonist plus hMG **Arm 2:** short GnRH antagonist plus clomif ne citrate and hMG
Outcomes	Clinical pregnancy rate
Notes	www.who.int/trialsearch/Tria 2 a px?TrialID=JPRN-UMIN000008760. Registration details not found. No author contact d tails nd.

Jutras 1990

Methods	Randomised on olled trial
Participants	**Incl sio crite ia:** first ART cycle
Interventions	**Ar 1:** c omifene citrate and hMG (n = ?) **Arm 2:** sh rt GnRH agonist plus hMG (n = ?)
Outcomes	Cancellation; oocyte number
Notes	Total number of participants unstated. Allocation unstated. No contact details for the authors. Awaiting classification.

Karabacak 2006

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age ≥35 years; ICSI treatment; day 2 baseline FSH <10IU/ml; baseline oestradiol <60 pg/ml; >4 follicles developed during COS; both ovaries present; no previous ovarian surgery or cystectomy; no endometriosis

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Karabacak 2006 *(Continued)*

Interventions	**Arm 1:** short GnRH antagonist (gonadotrophin unstated) **Arm 2:** long GnRH agonist (gonadotrophin unstated)
Outcomes	Oocyte number; miscarriage; live birth
Notes	Type of gonadotrophins used unstated, therefore unable to include. No contact details for the authors found.

Karatekeli 2004

Methods	Randomised controlled trial
Participants	**Inclusion:** age <36 years; first IVF cycle; normal day 3 FSH levels (<10 IU/l); no previous ovarian surgery; no previous endometriosis; no PCOS **Exclusion:** unstated
Interventions	**Arm 1:** "alternate day" GnRH agonist (gonadotrophin unstated) **Arm 2:** short GnRH antagonist (gonadotrophin unstated)
Outcomes	Clinical pregnancy
Notes	No details of gonadotrophins p ovided. Tming of GnRH agonist administration unclear. No up-to-date contact details for the au hor .

Kashani 2012

Methods	Randomised co trolled trial
Participants	**Inclusion cr teria:** age 21-39 years
Interventions	**Arm 1:** sh rt GnRH antagonist plus rFSH **Arm 2:** hort GnRH antagonist plus rFSH and hCG (formulation unstated)
Outcomes	Oocyte number
Notes	sufficient data in the abstract to extract. No up-to-date contact details found for the authors.

Kim 1997

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <40 years; normal SFA; tubal factor, endometriosis or anovulation
Interventions	**Arm 1:** long GnRH agonist plus hMG (n = ?) **Arm 2:** long GnRH agonist plus uFSH (n = ?)

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Kim 1997 *(Continued)*

Outcomes	Cancellation; oocyte number
Notes	Insufficient details in the abstract for inclusion. Full text not found.

Kingsland 1989

Methods	Randomised controlled trial
Participants	Women undergoing COS for ART
Interventions	**Arm 1:** hMG only (n = ?) **Arm 2:** clomifene citrate and hMG (n = ?) **Arm 3:** short GnRH agonist flare plus hMG (n = ?) **Arm 4:** long GnRH agonist plus hMG (n = ?)
Outcomes	Review outcomes not reported
Notes	Insufficient data from the abstract to include

Kyono 2005

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <40 years; <3 previous ART cycles; BMI <27 kg/m^2
Interventions	**Arm 1:** long GnRH gonist plus?FSH (n = 66) **Arm 2:** short GnRH antagonist plus?FSH (n = 63) **Arm 3:** shor GnRH antagonist plus hCG, unclear if FSH used (n = 63)
Outcomes	OHSS; ca cellation; oocyte number; clinical pregnancy
Notes	Insuffic nt data from the abstract - unable to tell type of gonadotrophin. It is likely that this is an addition to Kyono 2004, but impossible to know for sure. Also, groups A-C don't match the description of Kyono 2004.

Lee 2011a

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** <4 oocytes in previous ART cycle or AFC <5
Interventions	**Arm 1:** short GnRH antagonist plus letrozole and gonadotrophin (unspecified) (n = ?) **Arm 2:** short GnRH antagonist plus gonadotrophins (unspecified) (n = ?)
Outcomes	Oocyte number; live birth rate; miscarriage

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Lee 2011a *(Continued)*

Notes	Insufficient data from abstract to include. Author contact details not found.

Levy 1991

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Full text not found

Lisi 2002

Methods	Unstated
Participants	**Inclusion criteria:** normo-ovulatory women, baseline FSH <10 IU/L, no PCOS or hyperprolactinaemia
Interventions	**Arm 1:** long GnRH agonist plus FSH **Arm 2:** long GnRH agon st plus rFSH/rLH
Outcomes	Clinical pregnancy
Notes	Unclear if study randomised

Londra 2003

Methods	Unstated
Participants	**Inclusio criteria:** age <40 years; serum FSH <12 mIU/ml
Interventions	**Arm 1:** short GnRH antagonist plus rFSH with or without hMG (n = 49) **Arm 2:** long GnRH agonist plus rFSH with or without hMG (n = 212)
Outcomes	Oocyte number; clinical pregnancy
Notes	Unclear if study randomised. No contact details for trial authors.

Lopes 1987

Methods	Unclear
Participants	Unclear

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Lopes 1987 *(Continued)*

Interventions	Unclear
Outcomes	Unclear
Notes	Full text not found

Loutradis 2003

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Full text not f und

Ludwig 2003

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-35 year ; no previous low response; no untreated endocrinopathies
Interventions	**Arm 1:** short GnRH antagonist plus rFSH **Arm 2:** short GnRH antagon st plus rFSH and rLH
Outcomes	Oocyte number
Notes	Interim analysis

Machado 1999

Methods	Randomised controlled trial
Participants	Women undergoing COS for ART
Interventions	**Arm 1:** uFSH plus clomifene citrate and dexamethasone **Arm 2:** rFSH plus clomifene citrate and dexamethasone **Arm 3:** GnRH analogue plus uFSH **Arm 4:** GnRH analogue plus rFSH
Outcomes	Number of cleavage-stage embryos; miscarriage
Notes	Insufficient data from the abstract to include. Data expressed per cycle.

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Madani 2015

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** hyogonadotrophic hypogonadism
Interventions	**Arm 1:** rFSH (downregulation details unclear) **Arm 2:** rFSH and rLH (downregulation details unclear)
Outcomes	Oocyte number; clinical pregnancy
Notes	Insufficient data from abstract to include. No contact deta ls for a thors

Mahmoud 2001

Methods	Unstated
Participants	**Inclusion criteria:** male factor infertility
Interventions	**Arm 1:** long GnRH agonist plus rFSH **Arm 2:** long GnRH agonist plus rFSH and hMG
Outcomes	Oocyte number
Notes	Unclear if study randomised. Author contact details not found.

Malhotra 2013

Methods	Randomised co trol ed rial
Participants	**Inclusion c eria:** low-responding women as per Bologna criteria
Interventions	**Arm 1:** sh rt GnRH agonist flare (gonadotrophins unstated) **Arm 2** short GnRH antagonist (gonadotrophins unstated)
Outcomes	Cancellation; clinical pregnancy
Notes	Insufficient data in abstract to include. No author contact details.

Mansouri 2013

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** previous low ovarian response; ICSI
Interventions	**Arm 1:** "microdose GnRH agonist", gonadotrophins unclear (n = 32) **Arm 2:** short GnRH antagonist plus letrozole, unclear whether gonadotrophins included (n = 33)

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Mansouri 2013 *(Continued)*

Outcomes	Oocyte number
Notes	Full text not found

Marrs 2004

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <40 years; BMI <35 kg/m^2; normal response in previous IVF cycle
Interventions	**Arm 1:** short GnRH antagonist plus rFSH and hCG (formulation u stated) **Arm 2:** long GnRH agonist plus rFSH plus hCG (formulation unstated)
Outcomes	Oocyte number; ongoing pregnancy
Notes	Insufficient data in abstract to include. No au hor contact details.

Matallin 2011

Methods	Uncle r
Participants	Uncle r
Interventions	Unclear
Outcomes	Unclear
Notes	Full text not found

Mayenga 1997

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Full text not found

Miller 2009

Methods	Randomised controlled trial
Participants	Women undergoing COS for ART

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Miller 2009 *(Continued)*

Interventions	**Arm 1:** hMG (downregulation unstated) **Arm 2:** rFSH (downregulation unstated)
Outcomes	Ongoing pregnancy
Notes	Insufficient information from abstract. Interim analysis. No contact details for authors.

Moshin 2007

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** PCOS
Interventions	**Arm 1:** short GnRH antagonist plus rFSH **Arm 2:** long GnRH agonist plus rFSH
Outcomes	Ongoing pregnancy; OHSS
Notes	Insufficient data in abstract to include. Author contact details not found.

Motan 2011

Methods	Randomised controlled trial
Participants	Women undergoing COS fo ART
Interventions	**Arm 1:** GnRH agonist (timing unstated) plus hMG (n = ?) **Arm 2:** short Gn H antagonist plus hMG (n = ?) **Arm 3:** GnRH agonist (timing unstated) plus rFSH (n = ?) **A m 4:** short GnRH antagonist plus rFSH (n = ?) **Arm 5** GnRH agonist (timing unstated) plus rFSH and rLH (n = ?) **Arm 6:** short GnRH antagonist plus rFSH and rLH (n = ?)
Outcomes	Clinical pregnancy; oocyte number; cancellation
Notes	sufficient data in abstract to include. No author contact details.

Motta 2005

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** normo-ovulatory cycles
Interventions	**Arm 1:** short GnRH antagonist plus rFSH **Arm 2:** short GnRH antagonist plus rLH

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Motta 2005 *(Continued)*

	Arm 3: GnRH agonist (timing unstated) plus rFSH **Arm 4:** GnRH agonist (timing unstated) plus rLH
Outcomes	Review outcomes not reported
Notes	Insufficient data in abstract to include. No author contact details.

Nazzaro 2013

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** anovulation
Interventions	**Arm 1:** short GnRH antagonist plus rFSH alone (n 11) **Arm 2:** short GnRH antagonist plus rFSH and LH (n = 211
Outcomes	Oocyte number
Notes	Insufficient data in the abstract for extract on. No author contact details.

NCT00335725 2006

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18 <40 years; BMI 19-30 kg/m^2; <3 previous ART cycles; baseline FSH <10 IU/l within the 6 months prior to the study **Exclusion criter a:** age <18 years and ≥40 years; primary ovarian failure; low-responding women; oocyte donatio sy tem c diseases
Interventions	**Arm 1:** uFSH **Arm 2:** rF H
Outcomes	Oocyt number; clinical pregnancy
Notes	clinicaltrials.gov/show/NCT00335725. Status: completed as of 27 March 2015, but no publication found. No contact details for the authors found.

NCT00378001 20 6

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-<40 years; BMI 18-30 kg/m^2; <3 previous completed IVF cycles; baseline FSH <10 IU/l and oestradiol <80 pg/ml; normal uterus; AFC >10; normal thyroid function **Exclusion criteria:** low-responding women; PCOS; previous OHSS; inaccessible ovaries; ovarian cysts; hydrosalpinx; stage 3-4 endometriosis; oocyte donation; FET cycle; contraindications to pregnancy; abnormal bleeding; endocrine and neoplastic disorders

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NCT00378001 2006 *(Continued)*

Interventions	**Arm 1:** uFSH (downregulation unstated) **Arm 2:** rFSH (downregulation unstated)
Outcomes	Oocyte number; clinical pregnancy
Notes	https://clinicaltrials.gov/ct2/show/NCT00378001. Status update: recruitment completed 16 February 2015, no published data found.

NCT00417183 2006

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-39 yeas; BMI 18-29 kg/m^2; men trual cycle duration 24-35 days; normal baseline FSH, LH and oestradiol **Exclusion criteria:** low-responding women; COS
Interventions	**Arm 1:** long GnRH agonist (gonadotrophins unstated) **Arm 2:** short GnRH antagonist (gonadotrophins unstated)
Outcomes	Clinical pregnancy
Notes	https://clinicaltrials.gov/show/NCT 0417183. Last update 29 December 2006: recruitment. No published data.

NCT00485537 2007

Methods	Randomised co trolled rial
Participants	**Inclusion cr eria:** normal baseline FSH and oestradiol **Exc usion criter :** PCOS; endometriosis; exogenous LH administration
Interventions	**Arm 1:** hort GnRH antagonist (gonadotrophin unstated) **Arm 2:** GnRH agonist (timing of agonist unstated; gonadotrophin unstated)
Outcomes	Oocyte number; clinical pregnancy; miscarriage
Notes	ttps://clinicaltrials.gov/ct2/show/NCT00485537. Status: completed as of 13 June 2007. No published data found. No contact details found.

NCT00633555 2008

Methods	Randomised controlled trial - unclear
Participants	**Inclusion criteria:** age 21-44 years; low-responding women

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NCT00633555 2008 *(Continued)*

	Exclusion criteria: contraindications to oral contraceptive pill, injectable gonadotrophins, oestradiol or progesterone in oil; medical contraindications to pregnancy; prior IVF cycle with one of the interventions under study
Interventions	**Arm 1:** "microdose" GnRH agonist protocol (gonadotrophins unstated) **Arm 2:** "luteal phase" GnRH antagonist protocol (gonadotrophins unstated)
Outcomes	Oocyte number
Notes	Study registered as a "case-control" observational study. Status: Co pleted as of 25 May 2018, however no published results found.

NCT00677573 2008

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-44 years; at least on previous rial with adequate ovarian stimulation resulting in ≤4 oocytes **Exclusion criteria:** high-responding wom n
Interventions	**Arm 1:** short GnRH antagonist plus uFSH **Arm 2:** short GnRH antagonist plus rFSH
Outcomes	Oocyte number
Notes	Status unknown. Last updated 14 May 2008. clinicaltrials.gov/show/NCT00677573. Authors contacted on 16 September 2021 (mbahceci@superonline.com), reply awaited.

NCT00802360 2008

Methods	Random sed co trolled trial
Participants	**In lusion criteria:** age 18-42 years; BMI 18-34 kg/m^2; normal baseline serum FSH and oestradiol **Exclusion criteria:** gestational or surrogate carrier; donor oocyte; systemic diseases; ≥2 previous pregnancy losses; substance abuse; smoking; severe male factor
Interventions	**Arm 1:** short GnRH antagonist plus hMG **Arm 2:** short GnRH antagonist plus uFSH
Outcomes	Ongoing pregnancy; oocyte number; number of embryos cryopreserved; cancellation; clinical pregnancy
Notes	https://clinicaltrials.gov/ct2/show/NCT00802360. Status: Completed as of 2 November 2011. Results of the comparison Menopur vs Follistim requested from authors on 16 September 2021 (DK0-Disclosure@ferring.com). Reply awaited.

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NCT00805935 2008

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-42 years; PCOS (Roterdam criteria); BMI 18-39 kg/m^2; early follicular phase serum FSH and oestradiol within normal range; normal uterus and ovaries on ultrasound **Exclusion criteria:** gestational or surrogate carrier; donor oocyte; systemic diseases; ≥2 previous pregnancy losses; substance abuse; smoking; severe male factor
Interventions	**Arm 1:** short GnRH antagonist plus hMG **Arm 2:** short GnRH antagonist plus uFSH
Outcomes	Cancellation; oocyte number; clinical pregnancy; ongoing pr gnancy; live birth
Notes	https://clinicaltrials.gov/ct2/show/NCT00805935. Status Completed as of 27 January 2012. Results of the comparison Menopur vs Follistim requested from uthors on 16 September 2021 (DK0-Dis-closure@ferring.com). Reply awaited.

NCT00823004 2009

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** low response; at leas one previous failed IVF cycle; normal baseline serum oestradiol **Exclusion criteria:** baseline s rum FSH ≥12 mIU/ml
Interventions	**Arm 1:** short GnRH agonist flare plus rFSH or hMG **Arm 2:** short GnRH antagon st plus letrozole and rFSH or hMG
Outcomes	Review outcome not eported.
Notes	https://clinic ltria s gov/ct2/show/NCT00378001. Status: completed as of 16 February 2015. No published d ta found.

NCT00823602 2009

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <35 years; first ART cycle; baseline FSH <10 IU/l **xclusion criteria:** previous IVF or ICSI; endocrine anomalies; uterine anomalies; severe en-dometriosis; absence of one ovary
Interventions	**Arm 1:** long GnRH agonist plus rFSH **Arm 2:** short GnRH antagonist plus rFSH
Outcomes	Review outcomes not reported
Notes	https://clinicaltrials.gov/ct2/show/NCT00823602. Status: unknown as of 15 January 2009.

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NCT00830492 2009

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-35 years; regular menstrual cycles (26-35 days); baseline FSH <10 IU/l; BMI 18-30 kg/m^2; unexplained, mild male factor, tubal factor, early stage endometriosis or cervical factor **Exclusion criteria:** ICSI
Interventions	**Arm 1:** short GnRH antagonist plus clomifene citrate and rFSH **Arm 2:** long GnRH agonist plus rFSH
Outcomes	Clinical pregnancy
Notes	https://www.clinicaltrials.gov/ct2/show/NCT00830492. tatus: completed January 2009, no published data found.

NCT00883766 2009

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-37 years; PCOS (Rotterdam criteria); presence of both ovaries; absence of endometriomas on ultrasound; serum FSH <10 IUlL on day 3 of the menstrual cycle; normal oestradiol and progesterone at the start o stimulation **Exclusion criteria:** congenital rena hyperplasia; Cushing syndrome; androgen-producing tumours; endocrine dysfunctio ; serum FSH >10 mIU/ml
Interventions	**Arm 1:** long GnRH agonist p us rFSH **Arm 2:** short GnRh antagonist plus rFSH
Outcomes	Clinical pregnanc OHSS
Notes	http ://c nical ials.gov/ct2/show/NCT00883766. Status: terminated as of 20 July 2012. No published dat found. No contact details found.

NCT00894608 2009

Methods	Randomised controlled trial
Participants	**nclusion criteria:** PCOS
Interventions	**Arm 1:** letrozole plus gonadotrophins (downregulation and gonadotrophins unstated) **Arm 2:** long GnRH agonist plus gonadotrophins (unstated)
Outcomes	Cancellation; oocyte number; clinical pregnancy; OHSS
Notes	clinicaltrials.gov/show/NCT00894608 Recruitment status: unknown Last updated May 2009 (enrolling by invitation)

Preview

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NCT01016210 2009

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 25-45 years
Interventions	**Arm 1:** short GnRH antagonist plus rFSH **Arm 2:** short GnRH antagonist plus rFSH and rLH
Outcomes	Review outcomes not reported
Notes	https://clinicaltrials.gov/ct2/show/NCT01016210. Status: Completed as of 17 January 2014. No published data found. No contact details found.

NCT01071200 2010

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-40 years; regular menstrual cycles (25-35 days); BMI ≤28 kg/m^2; normal serum prolactin; both ovaries visible on ultr sound; only one previous IVF/ICSI cycle **Exclusion criteria:** oligo/anovulatory cy les; male partner azoospermia; baseline FSH >10 IU/l; abnormal cervical cytology; abnormal uter bleeding; systemic conditions
Interventions	**Arm 1:** rFSH and rLH (downregula ion nstated) **Arm 2:** rFSH (downregulation unstated)
Outcomes	Oocyte number; clinical pregnancy; OHSS
Notes	https://clinicalt als.gov/ct2/show/NCT01071200. Status: completed as of 27 December 2013. Additional informati n eque ted from authors (service@merckgroup.com) on 16 September 2021, reply on 30 Se temb r stating results not yet published.

NCT01079949 2010

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** premenopausal woman, aged 35-42 years wanting to become pregnant; subjects with FSH baseline plasma levels less than or equal to 10 IU/l (Day 2-5 of the cycle) and with H and E2 levels within the normal limits of the local laboratory; subjects having regular spontaneous menstrual cycle lasting 25-35 days; infertility that is susceptible to treatment with IVF/ICSI; COS protocol with rFSH and GnRH antagonist; partner's sperm suitable for IVF/ICSI according to local laboratory, unless using sperm donor; uterine cavity capable of sustaining the implantation of embryo or carrying a pregnancy; normal pap smear (papanicolaou) 6 months prior to be included in the study (signature of informed consent); BMI <30 kg/m^2 at the beginning of ovarian stimulation; confirmed absence of pregnancy with beta-hCG test (urine or blood) before starting the administration of rFSH; willing to adjust to the protocol for the entire duration of the study; informed consent prior to any study-related procedure that is not part of normal medical care **Exclusion criteria:** known positivity for HIV, HBV or HCV or Hepatitis-B /Hepatitis-C virus (HBV/HCV); any systemic illnesses of clinical significance, hypothalamus and pituitary tumors; cancer of ovaries, uterus or breast; hormonal anomalies and/or medical, biochemical, haematological illnesses that, according to the investigator, could interfere with the treatment with gonadotropins;

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NCT01079949 2010 *(Continued)*

	more than 2 previous ART cycles; cancelled two previous ART cycles; frozen embryos from previous ART cycles; non-specific gynaecological bleeding; polycystic ovaries, increased in size or with cysts of unknown etiology; any contraindication for becoming pregnant and/or carrying pregnancy to term; known allergy to gonadotrophin preparations or any of the excipients; drug dependence or history of drug or alcohol abuse in the previous 5 years; previously entered into this study or simultaneous participation in another clinical drug trial with drugs; unwilling to or not being able to adjust to the study protocol
Interventions	**Arm 1:** short GnRH antagonist plus rFSH and rLH **Arm 2:** short GnRh antagonist plus rFSH
Outcomes	Oocyte number; OHSS; cancellation; clinical pregnancy
Notes	https://clinicaltrials.gov/ct2/show/NCT01079949. Status: t l term ated as of February 2014 due to low recruitment date, no published data found.

NCT01110707 2010

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 35-40 years; low ovar an reserve **Exclusion criteria:** contraindications to reatment
Interventions	**Arm 1:** long GnRH agonist plus rFSH **Arm 2:** long GnRH agonist plus rFSH and rLH
Outcomes	Oocyte number; clinical pr gnancy; cancellation
Notes	https://clinicaltrials gov/ct2/show/NCT01110707. Status: completed as of 27 March 2018, results not found.

NCT01213147 2010

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age ≥38 years; one or more previous failed IVF cycles **E clusion criteria:** BMI >30 kg/m^2; endocrine disorders; metabolic disorders; previous ovarian surgery; severe endometriosis; severe male factor
Interventions	**Arm 1:** clomifene citrate **Arm 2:** buserelin
Outcomes	Clinical pregnancy
Notes	https://clinicaltrials.gov/ct2/show/NCT01213147. Status: Completed as of 1 October 2010. No published data found. No contact details found for the authors.

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NCT01337531 2011

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-40 years; PCOS; primary infertility **Exclusion criteria:** secondary infertility
Interventions	**Arm 1:** rFSH (downregulation unstated) **Arm 2:** uFSH (downregulation unstated)
Outcomes	Review outcomes not reported
Notes	https://clinicaltrials.gov/ct2/show/NCT01337531. Status: enr lling by inv tation as of 19 April 2011. No published data found. No contact details found.

NCT01354275 2011

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-35 years; PCOS **Exclusion criteria:** age >35 years; end crinopathies other than PCOS; >2 previous ART cycles; previous and current use of metformin
Interventions	**Arm 1:** long GnRH agonist plus FSH **Arm 2:** short GnRH antagonist lus rFSH
Outcomes	Ongoing pregnancy; clini al preg ancy; OHSS
Notes	clinicaltrials.gov/show/NCT 354275. Trial terminated, no results published.

NCT01402336 2011

Methods	R ndomi ed controlled trial
Participants	**Inclusio criteria:** age 20-40 years; PCOS (Rotterdam criteria); normal uterus; Korean ethnicity **Exclusion criteria:** endocrinopathy other than PCOS; previous adverse events from rFSH
Interventions	**Arm 1:** short GnRH antagonist (commenced with stimulation) plus rFSH **rm 2:** short GnRH antagonist (commenced from day 6 of stimulation) plus rFSH **Arm 3:** long GnRH agonist (gonadotrophins unstated)
Outcomes	Oocyte number
Notes	clinicaltrials.gov/show/NCT01402336. Recruitment completed but no published data found. No contact details for the authors available.

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NCT01565265 2012

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-35 years; BMI 19-30 kg/m^2; male infertility; cycle length 27-32 days; presence of both ovaries; rubella immunity **Exclusion criteria:** age >35 years; pregnancy and breast feeding; ovarian endometriosis; uterine fibroids; surgical sperm retrieval
Interventions	**Arm 1:** long GnRH agonist plus rFSH/rLH **Arm 2:** short GnRH antagonist plus rFSH/rLH
Outcomes	OHSS; miscarriage
Notes	https://clinicaltrials.gov/ct2/show/NCT01565265. Status recr itment completed as of 1 May 2017 but no published data found. No contact details found.

NCT01577199 2012

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-42 years; AF < and AMH <0.5 ng/ml and/or prior low response to COS **Exclusion criteria:** BMI >30 kg/m^2; prei p antation genetic diagnosis; age >42 years; fragile X carriers; testicular sperm extraction; A erman syndrome; untreated hydrosalpinx; >6 prior ART cycles
Interventions	**Arm 1:** short GnRH antagonist p us clomifene citrate and uFSH or hMG **Arm 2:** short GnRH antag nist pl s uFSH or hMG
Outcomes	Review outcomes not report d
Notes	https://clinicalt als gov/ct2/show/NCT01577199. Status: withdrawn (no subjects recruited) as of 16 December 2016.

NCT01669291 2012

Methods	Randomised controlled trial
Participants	**I clusion criteria:** age 21-40 years; baseline FSH <10 IU/l; AFC 5-20; BMI 18-32 kg/m^2 **xclusion criteria:** PCOS; smoking; endometriosis; surgical sperm retrieval
Interventions	**Arm 1:** long GnRH agonist plus uFSH/hMG **Arm 2:** short GnRH antagonist plus uFSH/hMG
Outcomes	Review outcomes not reported
Notes	clinicaltrials.gov/show/NCT01669291. Last update: 4 June 2014, completed but no published data. No contact details found.

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NCT01922193 2013

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-39 years; Chinese ethnicity; BMI 18.5-28 kg/m^2; tubal, unexplained or male factor infertility; regular menstrual cycles **Exclusion criteria:** low ovarian response; OHSS; PCOS; endometriosis
Interventions	**Arm 1:** uFSH **Arm 2:** rFSH
Outcomes	Oocyte number; cancellation; clinical pregnancy; ongoing preg ncy
Notes	clinicaltrials.gov/show/NCT01922193. No data published found. L st update 16 June 20215. No contact details for the authors available.

NCT01926210 2013

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <45 years; low-responding women; BMI 18-35 kg/m^2; regular menstrual cycles (23-35 days) **Exclusion criteria:** previous >2 failed A T ycles; serious adenomyosis; PCOS; abnormal uterus; systemic disease
Interventions	**Arm 1:** short GnRH antagonist p us letrozole and rFSH **Arm 2:** long GnRH agonis plus rFSH
Outcomes	Clinical pregnancy; live birth; oocyte number; ongoing pregnancy; OHSS
Notes	clinicaltrials.go /ct2/show/NCT01926210 Last update 21 August 2013: not yet recruiting. Authors contacted o 16 S ptember 2021 (dengyu1983@yahoo.com.cn), reply awaited.

NCT01948804 2013

Methods	Randomised controlled trial
Participants	clusion criteria: age 18-44 years; AMH <1.1 ng/ml and/or previous low ovarian response; primary infertility; BMI ≤30 kg/m^2
Interventions	**Arm 1:** short GnRH antagonist plus letrozole **Arm 2:** microdose GnRH agonist flare protocol plus rFSH **Arm 3:** short GnRH antagonist plus clomifene citrate **Arm 4:** short GnRH antagonist protocol (gonadotrophin unstated)
Outcomes	Clinical pregnancy; oocyte number
Notes	https://clinicaltrials.gov/ct2/show/NCT01948804. Status: Not yet recruiting as of 15 January 2014. No contact details found.

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NCT01969201 2013

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-38 years; BMI 18-28 kg/m^2; <3 previous ART cycles; baseline FSH <10 IU/l and oestradiol <80 pg/ml; normal TSH, AMH and AFC levels **Exclusion criteria:** low ovarian reserve; PCOS; previous OHSS; uterine malformations; ovarian cysts; hydrosalpinx; endometriosis stage 3 or 4; oocyte donation; severe male factor; hypersensitivity to study medication
Interventions	**Arm 1:** short GnRH antagonist plus uFSH **Arm 2:** short GnRh antagonist plus rFSH
Outcomes	Clinical pregnancy; oocyte number; live birth
Notes	Insufficient data (e.g. unclear which antagoni t used, how allocation was performed) to include in current format. Emailed for further informat n rd@ibsa. h on 9 February 2021, reply awaited.

NCT02070198 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 25 to 4 yea ; low predicted response **Exclusion criteria:** BMI >30 kg/ 2; PCOS; stage 3-4 endometriosis; inflammatory or autoimmune disorders; metabolic disease; fertility treatment within the past two months
Interventions	**Arm 1:** short GnRH antagon st plus long acting rFSH **Arm 2:** short GnRH an agonist plus daily rFSH **Arm 3:** short GnRH agon st flare plus rFSH
Outcomes	Clini al pregna cy
Notes	h ps://c inicaltrials.gov/ct2/show/NCT02070198. Status: recruiting as of 25 February 2014; recruitment atus currently unknown. Authors emailed for further information on 16 September 2021 (bioroma@bioroma.net), reply awaited.

NCT02118051 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age ≥18 years; low predicted response **Exclusion criteria:** anovulation; untreated tubal or uterine pathology; severe male factor
Interventions	**Arm 1:** short GnRH antagonist plus rFSH **Arm 2:** short GnRH antagonist plus hMG
Outcomes	Review outcomes not reported

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NCT02118051 2014 *(Continued)*

Notes	clinicaltrials.gov/show/NCT02118051. Last update: completed on 12 June 2017, but no published data found. No contact details for the authors found.

NCT02128360 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-43 years; low predicted response **Exclusion criteria:** preimplantation genetic diagnosis; do or egg atment
Interventions	**Arm 1:** short GnRH antagonist plus letrozole and gonadotr phins (nspecified) **Arm 2:** short GnRH antagonist plus gonadotrophins (un pecified)
Outcomes	Clinical pregnancy; oocyte number
Notes	https://clinicaltrials.gov/show/NCT02128360. st update November 2014 - unknown. No contact details found.

NCT02173977 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20 5 yea p to three previous IVF attempts **Exclusion criteria:** low or o response in previous COS cycles; abnormal ovarian reserve markers (AMH, AFC)
Interventions	**Arm 1:** ultrasho t GnRH agonist/antagonist plus gonadotrophins (unspecified) **Arm 2:** short GnRH ant gonist plus gonadotrophins (unspecified)
Outcomes	Ongoing regnancy; clinical pregnancy; multiple pregnancy; miscarriage; oocyte number; OHSS
Notes	https:/ clinicaltrials.gov/ct2/show/NCT02173977. Status: unknown as of 25 June 2014. No contact details und.

NCT02237755 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** low response to ovarian stimulation
Interventions	**Arm 1:** short GnRH antagonist plus clomifene citrate and hMG **Arm 2:** short GnRH antagonist plus hMG
Outcomes	Clinical pregnancy
Notes	https://clinicaltrials.gov/ct2/show/NCT02237755. Status: not yet recruiting as of 11 September 2014.

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NCT02254928 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age ≥40 years; previous low ovarian response (≤3 oocytes); low ovarian reserve (AFC <5-7 follicles; AMH <0.5-1.1 ng/ml)
Interventions	**Arm 1:** rFSH and hMG (downregulation unspecified) **Arm 2:** rFSH only (downregulation unspecified)
Outcomes	Oocyte number
Notes	https://clinicaltrials.gov/show/NCT02254928. Trial terminated due to lack of funding. Updated 18 January 2016.

NCT02342197 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age >35 years; day 3 serum FSH >10 mIU/ml; AFC <6; small ovarian volume; AMH <1 ng/ml; prior low ovarian response to COS **Exclusion criteria:** PCOS; endometrios ; ormal response to COS; ovarian cyst
Interventions	**Arm 1:** short GnRH agonist fla e (gonadotrophins unspecified) **Arm 2:** long GnRH agonist (g nadotrophins unspecified)
Outcomes	Oocyte number
Notes	https://www.clinicalt ials.gov/ct2/show/NCT02342197. Status: completed as of 28 January 2015. No results foun No con act details found.

NCT02418533 2015

Methods	Random ed controlled trial
Participants	**Inclusion criteria:** age 21-38 years; normal baseline hormones; AMH >1.5 ng/ml; AFC 10-20; body weight >50 kg **xclusion criteria:** PCOS; smoking; endometriosis; surgical sperm retrieval; donor egg cycles.; preimplantation genetic testing
Interventions	**Arm 1:** hMG (downregulation unstated) **Arm 2:** rFSH (downregulation unstated)
Outcomes	Embryo quality
Notes	https://clinicaltrials.gov/ct2/show/NCT02418533. Status: Completed as of 12 August 2020. No published data found. Author contact details not found.

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NCT02429999 2015

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-35 years; unexplained infertility or tubal factor; BMI 18-29 kg/m^2; AFC >5 in one ovary; normal SFA **Exclusion criteria:** endometriosis; azoospermia; BMI >29 kg/m^2
Interventions	**Arm 1:** letrozole plus FSH **Arm 2:** long GnRH agonist plus FSH
Outcomes	Oocyte number
Notes	Status: "unknown" as of 19 March 2022. https://clinicaltrials.gov/ct2/show/NCT02429999

NCT02741154 2016

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-44 years; ovar an, tubal or unexplained infertility; low ovarian response **Exclusion criteria:** predicted high esponse; endometriosis; male and uterine factor; ovarian mass or cyst
Interventions	**Arm 1:** short GnRH antagoni t plus letrozole and hMG **Arm 2:** short GnRH antagon st plus hMG
Outcomes	Oocyte quality
Notes	https://clinic ltri s gov/ct2/show/NCT02741154. Status: completed as of 6 September 2017. No published data found.

NCT02785822 2016

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-38 years; BMI <30 kg/m^2; PCOS (Rotterdam criteria); baseline FSH ≤10 IU/ presence of both ovaries and normal uterus **Exclusion criteria:** severe male factor; low ovarian reserve; endocrinopathy; blood-borne infections
Interventions	**Arm 1:** hMG (downregulation unstated) **Arm 2:** uFSH (downregulation unstated)
Outcomes	Review outcomes not reported
Notes	https://clinicaltrials.gov/ct2/show/NCT02785822. Status: terminated as of 25 February 2019 due to difficulties in recruitment.

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NCT02940535 2016

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 35 to 45 years; low predicted response to COS **Exclusion criteria:** contraindications for IVF/ICSI; contraindications to pregnancy; primary ovarian insufficiency; AFC <3; preimplantation genetic testing
Interventions	**Arm 1**: long GnRH agonist plus hMG/hCG **Arm 2:** short GnRH agonist flare hMG/hCG
Outcomes	Live birth; clinical pregnancy; multiple pregnancy; miscarriage; e topic pr gnancy; oocyte number
Notes	https://clinicaltrials.gov/ct2/show/NCT02940535. Status not yet recruiting as of 21 October 2016. Authors emailed on 16 September 2021 for further informa ion (wangyh85@foxmail.com), reply awaited.

NCT03177538 2017

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 35-41 years; BMI 7 5-30 kg/m^2; predicted low response to COS; early follicular phase serum FSH ≤15 IU/l **Exclusion criteria:** preexisting edical conditions; abnormal IVF infection screening; uterine pathology; ovarian cysts
Interventions	**Arm 1:** short GnRH antagon st plus rFSH and hMG **Arm 2:** short GnRH a tagonist plus rFSH and rLH
Outcomes	Oocyte numb r; ncellation; clinical pregnancy
Notes	http ://c nical ials.gov/ct2/show/NCT03177538. Stauts: completed 12 September 2019, no data published

NCT03208972 2014

Methods	Randomised controlled trial
Participants	**nclusion criteria:** age 18-38 years **Exclusion criteria:** PCOS or other endocrinopathies
Interventions	**Arm 1:** rFSH and hCG (downregulation unspecified) **Arm 2:** rFSH and uFSH (downregulation unspecified)
Outcomes	OHSS
Notes	clinicaltrials.gov/show/NCT03208972. Recruitment completed 3 February 2021, no data published as of 14 September 2021.

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NCT04193930 2019

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 40-45 years; previous low response; abnormal ovarian reserve tests **Exclusion criteria:** women with high or normal response; endocrine or metabolic diseases; severe male factor; systemic diseases
Interventions	**Arm 1:** letrozole plus hMG (downregulation unspecified) **Arm 2:** hMG plus rFSH (downregulation unspecified)
Outcomes	Review outcomes not reported
Notes	No contact details found for the authors. https://clinicaltrials.gov/ct2/show/NCT04193930 Status unknown as of 19 March 2022 (last up ated on 10 ecember 2019).

NTR2593 2010

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** women un ergoing COS for ART
Interventions	**Arm 1:** short GnRH antagon st plus uFSH/rFSH **Arm 2:** long GnRH agonist plus hMG
Outcomes	Ongoing pregnan y; linical pregnancy; multiple pregnancy; miscarriage; oocyte number; number of embryos cryopres rv d; cancellation
Notes	www.who.in /trialsearch/Trial2.aspx?TrialID=NTR2593. Trial register status as "planned" as of 14 Septe ber 2021

O'Dea 1993

Methods	Randomised controlled trial
Participants	nclusion criteria: age 18-38 years; normo-ovulatory cycles; tubal factor, unexplained or endometriosis-associated infertility; endocrinologically normal
Interventions	**Arm 1:** long GnRH agonist plus uFSH (n = ?) **Arm 2:** long GnRH agonist plus rFSH (n = ?)
Outcomes	Oocyte number; number of cleavage-stage embryos; clinical pregnancy; ongoing pregnancy
Notes	Interim analysis. Insufficient data in the abstract to include. No contact details for the authors found.

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Ozdogan 2012

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** low-responding women
Interventions	**Arm 1:** short GnRH antagonist plus gonadotrophins (unspecified) (n = 50) **Arm 2:** short GnRH agonist flare plus gonadotrophins (unspecified) (n = 50)
Outcomes	Oocyte quality; clinical pregnancy
Notes	Insufficient data in the abstract to include. Author contact details ot found.

PACTR201411000933365 2014

Methods	Unstated
Participants	**Inclusion criteria:** normal gonadotrophin levels; PCOS (Rotterdam criteria); BMI <35 kg/m^2
Interventions	Interventions unclear
Outcomes	Oocyte number; clinical pregnancy
Notes	www.who.int/trialsearch/Trial2 aspx?TrialID=PACTR201411000933365. Status: completed as of 10 July 2018. No results available No aut or contact details.

PACTR201704002212265 2017

Methods	Unstated
Participants	**Inclusion cr teria:** gular menstrual cycles (21-35 days); BMI <30 kg/m^2; low ovarian response (Bologna crit ria)
Interventions	**A m 1:** short GnRH antagonist (gonadotrophins unstated) **Arm 2:** hort GnRH agonist flare (gonadotrophins unstated)
Outcomes	Oocyte number
Notes	ww .who.int/trialsearch/Trial2.aspx?TrialID=PACTR201704002212265. Status: completed as of 15 pril 2017. No results available. No author contact details.

Rag 2012

Methods	Unclear
Participants	Unclear
Interventions	Unclear

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Rag 2012 *(Continued)*

Outcomes	Unclear
Notes	Full text not found

RBR-736jwh 2019

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	www.who.int/trialsearch/Trial2.aspx?T ialID=RB 736jwh. No trial details found.

Righini 1998

Methods	Unclea
Participants	Unclea
Interventions	Uncle r
Outcomes	Unclear
Notes	Full text not found

Saini 2010

Methods	Ra domised controlled trial
Participants	Wome undergoing COS for ART
Interventions	**Arm 1:** short GnRH antagonist plus rFSH/rLH **A m 2:** long GnRH agonist plus gonadotrophins (unstated)
Outcomes	Oocyte number
Notes	Insufficient data in the abstract for extraction. No author contact details.

Santonastaso 2020

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** low ovarian response

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Santonastaso 2020 *(Continued)*

	Exclusion criteria: PCOS; endometriosis; metabolic and endocrine diseases; severe oligoasthenoteratozoospermia
Interventions	**Arm 1:** short GnRH antagonist plus rFSH/rLH (n = ?) **Arm 2:** short GnRH antagonist plus rFSH (n = ?)
Outcomes	Oocyte number
Notes	Insufficient data in the abstract regarding the number of participants allocated to each arm. No contact details for trial authors.

Scheffler 2015

Methods	Randomised controlled study
Participants	**Inclusion criteria:** low-responding women (ologna criteria)
Interventions	**Arm 1:** short GnRH agonist flare plus FSH or hMG (S formulation unstated, n = ?) **Arm 2:** short GnRH antagonist plus FSH o hMG (FSH formulation unstated, n = ?)
Outcomes	Ongoing pregnancy; cancellation; num er of eavage-stage embryos
Notes	Author contact details not found

Shah 2014

Methods	Randomised controlled trial
Participants	**Inclusion criter a:** age < 7 years
Interventions	**Arm 1:** "standard" GnRH analogues (gonadotrophins unstated) **A m 2:** ar matase inhibitor and gonadotrophins (downregulation unstated)
Outcomes	Oocyte umber; number of cleavage-stage embryos; live birth
Notes	Insufficient information from abstract to include

Sills 1999

Methods	Randomised controlled trial, although unclear whether all participants were randomised
Participants	**Inclusion criteria:** age 30-41 years; BMI 18-35 kg/m^2 **Exclusion criteria:** history of endocrinopathy or other illness; >3 prior gonadotrophin treatments for IVF; gonadotrophin use within previous 6 months
Interventions	**Arm 1:** long GnRH agonist plus uFSH **Arm 2:** long GnRH agonist plus uFSH and rLH

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Sills 1999 *(Continued)*

Outcomes	Clinical pregnancy; ongoing pregnancy; oocyte number
Notes	One patient underwent a second cycle but unclear if randomised to that arm. Unclear if truly randomised study for all participants. Study authors emailed on 16 September 2021 (dr.sills@ivf.com), reply awaited.

Soong 1999

Methods	Randomised controlled trial
Participants	Women undergoing COS for ART
Interventions	**Arm 1:** rFSH (downregulation unstated) **Arm 2:** uFSH (downregulation unstated)
Outcomes	Oocyte number; ongoing pregnancy
Notes	Insufficient data regarding pituitary suppression in both groups. No contact details.

Streda 2009

Methods	Randomised controlled trial
Participants	Unselected sample of wome undergoing COS for ART
Interventions	**Arm 1:** GnRH agonist (timin unstated) plus rFSH or hMG **Arm 2:** short GnRH a tagonist plus rFSH or hMG
Outcomes	Review outcome not reported
Notes	Article in Czech Outcomes of interest not reported. Authors emailed on 16 September 2021 (rstreda@seznam.cz), reply awaited.

Tanaka 2009

Methods	Randomised controlled trial
Participants	**nclusion criteria:** age <40 years
Interventions	**Arm 1:** short GnRH antagonist plus hMG (n = ?) **Arm 2:** short GnRH agonist flare plus hMG (n = ?) **Arm 3:** long GnRH agonist plus hMG (n = ?)
Outcomes	Review outcomes not reported
Notes	Insufficient data in the abstract to extract. No contact details found.

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Tanaka 2014

Methods	Randomised controlled trial
Participants	Women undergoing COS for ART
Interventions	Unclear - "mild stimulation" versus "controlled stimulation"
Outcomes	Miscarriage
Notes	Insufficient data in the abstract to extract. No contact details found.

Tasdemir 1995

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Uncle r
Notes	Full t xt not found

The US GonalF Clinical Trial Group 1999

Methods	Randomised controlled trial
Participants	**Included criter a:** only ICSI patients with male factor infertility
Interventions	**Arm 1:** long GnRH agonist plus rFSH (n = ?) **Arm 2:** lo g GnRH agonist plus rFSH/rLH (n = ?)
Outcomes	Clin cal pregnancy
Notes	Insufficient data in the abstract to extract. No contact details found.

The US Multicenter tudy I vestig tor Group 1998

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Full text not found

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Toporcerová 2005

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <40 years; BMI 20-25 kg/m^2; FSH <10 IU/l **Exclusion criteria:** <2 ovaries; prior ovarian surgery; male, tubal or unexplained infertility
Interventions	**Arm 1:** GnRH agonist plus rFSH (timing of GnRH agonist unstated) **Arm 2:** GnRH agonist plus rFSH and hMG (timing of GnRH agonist uns ated) **Arm 3:** GnRH agonist plus rFSH and rLH (timing of GnRH agonist unsta d)
Outcomes	Oocyte number; clinical pregnancy; ongoing pregnancy
Notes	Article in Czech - translation facilitated by Dr Petr Tomek. No contact details for the authors.

Tosun 2022

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** low ovarian response (according to Bologna criteria) **Exclusion criteria:** male factor p imary ovarian failure, need for preimplantation genetic diagnosis
Interventions	All women underwent microdose flare-up GnRH agonist stimulation protocol or GnRH antagonist stimulation protocol
Outcomes	Oocyte number
Notes	Women underw nt either micro-dose agonist flare or GnRH antagonist protocol. Details of which women unde wen whi h type of downregulation were not provided. Authors contacted on 16 September 021 (sebnem_alanya@hotmail.com), reply awaited.

Turkcapar 2009

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** PCOS (Rotterdam criteria)
Interventions	**Arm 1:** GnRH analogue plus hMG (unclear analogue formulation and timing) **Arm 2:** GnRH analogue plus rFSH (unclear analogue formulation and timing)
Outcomes	OHSS
Notes	Insufficient data from the abstract to include. Author contact details not found.

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van de-Helder 1990

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Abstract text not found

Weathersbee 1999

Methods	Randomised controlled trial
Participants	Women undergoing COS for ART
Interventions	**Arm 1:** long GnRH agonist plus rFSH (n = ?) **Arm 2:** long GnRH agonist plus rFSH/rLH (n = ?)
Outcomes	Oocyte number; clinical pregnancy
Notes	Insufficient data in the abstract to in lude (number of patients in each arm not specified)

Yanping 2012

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Full text not found

Youssef 2010

Methods	nclear if randomised
Participants	**Inclusion criteria:** age 20-43 years; primary or secondary infertility; normal menstrual cycle; BMI <27 kg/m^2; no fertility medication within the previous 1.5 months; both ovaries present; basal day 3 FSH <10 IU/l
Interventions	**Arm 1:** long GnRH agonist plus hMG **Arm 2:** short GnRH antagonist plus clomifene citrate and hMG
Outcomes	Cancellation; oocyte number; clinical pregnancy

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Youssef 2010 *(Continued)*

Notes	Insufficient data in the abstract to include. Status unclear.

Zeinalzadeh 2014

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** PCOS
Interventions	**Arm 1:** short GnRH antagonist **Arm 2:** GnRH agonist (timing of agonist unstated)
Outcomes	OHSS; oocyte number
Notes	Insufficient data in the abstract to extract. No contact details found.

Zeinalzadeh 2014a

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** predicted low response
Interventions	**Arm 1:** GnRH agonist protoco (timing nstated) **Arm 2:** short GnRH antagon st pro col
Outcomes	Cancellation; oocyte numb r; clinical pregnancy
Notes	Insufficient data from abstract to include

AFC, antral follicle count; AMH, anti-Müllerian hormone; ART, assisted reproductive technology; ASRM, American Society of Reproductive Medicine; BMI, body mass index; COS, c rolled ovarian stimulation; ET, embryo transfer; FSH, follicle stimulating hormone; GnRH, gonadotrophin-releasing hormone; H V, hepatitis B virus; HCV, hepatitis C virus; hCG, human chorionic gonadotrophin; HIV, human immunodeficiency virus; hMG, hum n men pausal gonadotrophin; HP-hMG, highly purified human menopausal gonadotrophin; ICSI, intracytoplasmic sperm injection; IM, in muscular administration; IVF, in vitro fertilisation; IVM, in vitro maturation; LH, luteinising hormone; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening POM, polycystic ovarian morphology; RCT, randomised controlled trial; rFSH, recombinant follicle stimulating hormone; rhCG, recombinant human chorionic gonadotrophin; rLH, recombinant luteinising hormone; SC, subcutaneous administration; SFA, seminal fluid a alysis; TESE, testicular sperm extraction; TSH, thyroid-stimulating hormone; uFSH, urinary follicle stimulating hormone; uhCG urina y human chorionic gonadotrophin

Characteristics of ongoing stu ies *[ordered by study ID]*

ChiCTR1800016257 18

Study name	Application of ovarian stimulation based on the age in patients with poor ovarian response
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** low ovarian response

Preview

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ChiCTR1800016257 2018 *(Continued)*

	Exclusion criteria: BMI>29 or <18.5 kg/m^2; COS within the previous three months; endometriosis,hyperprolactinaemia, endocrine or metabolic disease; history of ovarian excision or radiotherapy; chromosomal abnormalities
Interventions	**Arm 1:** "minimal stimulation" **Arm 2:** GnRH antagonist protocol **Arm 2:** GnRH agonist protocol
Outcomes	Clinical pregnancy; cancellation
Starting date	Registered on 22 May 2018 Status: recruiting as of 19 March 2022 (last updated 28 May 2018)
Contact information	scdb@126.com
Notes	www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR180 016257

ChiCTR1800018077 2018

Study name	LH based flexible GnRH antagonist pro ocol in women with normal ovarian response undergoing in vitro fertilization and embryo transfer: a r ndomized controlled trial
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 23- 5 year ; egular menstrual cycles; baseline FSH <10 IU/l, AFC 8-20; BMI 18-23 kg/m^2 **Exclusion criteria:** PC S ut rine malformations; endometriosis; adenomyosis; systemic comorbidities
Interventions	**Arm 1:** tradition l exib e GnRH antagonist protocol **Arm 2:** "mor flexible" GnRH antagonist protocol based on serum LH level
Outcomes	OHSS; cli ical pregnancy
Starting date	Register d on 29 August 2018 Status: recruiting as of 19 March 2022 (last updated 6 July 2020)
Contact information	lius an821009@126.com
Notes	ttps://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR1800018077

ChiCTR1800018129 2018

Study name	LH based flexible GnRH antagonist protocol in PCOS patient undergoing in vitro fertilization and embryo transfer: a randomized controlled trial
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 23-35 years; PCOS (Rotterdam criteria); BMI 18-28 kg/m^2

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ChiCTR1800018129 2018 *(Continued)*

	Exclusion criteria: uterine anomaly; endometriosis; adenomyosis; medical comorbidities
Interventions	**Arm 1:** traditional flexible GnRH antagonist protocol **Arm 2:** LH-based flexible GnRH antagonist protocol
Outcomes	Clinical pregnancy; OHSS
Starting date	Registered on 31 August 2018 Status: recruiting as of 19 March 2022 (last updated on 29 June 2020
Contact information	liushan821009@126.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR180 18129

ChiCTR1800018246 2018

Study name	GnRH antagonist and progestin used for prevent g pr mature ovulation in infertile women during IVF/ICSI treatment: a prospective randomized controlled trial
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-40 years; BMI 18 30 kg/m^2; tubal, male or unexplained infertility; normal ovarian reserve; normal menstrual ycles (25-35 days); AFC 8-20; baseline FSH <10 IU/l; AMH >1.1 ng/ml; first IVF cycle **Exclusion criteria:** system dise ; endometriosis grade 3 or higher; PCOS; hydrosalpinx; reproductive tract tumours; abnorm l karyotype; uterine anomalies; cervical incompetence; recurrent pregnancy loss; baseline oestradiol >80 pg/ml; functional ovarian cysts on ultrasound
Interventions	**Arm 1:** PPOS prot c l **Arm 2:** GnRH-a dr g un tated) protocol
Outcomes	Live bi th; miscarriage; ongoing pregnancy; oocyte number
Starting date	R gistered on 6 September 2018 Status: cruiting as of 19 March 2022 (last updated on 10 September 2018)
Contact information	christinqy@163.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR1800018246

ChiCTR1900021266 2 19

Study name	Clinical comparison of long acting agonist protocol and short acting agonist protocol of in vitro fertilization and embryo transfer: a randomized controlled trial
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** women undergoing COS for ART

Preview

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ChiCTR1900021266 2019 *(Continued)*

	Exclusion criteria: BMI >19 or <18 kg/m^2; COS within the preceding three months; endometriosis; hyperprolactinaemia; endocrine disease; metabolic disease; previous ovarian excision or radiotherapy; chromosomal abnormalities
Interventions	**Arm 1:** long acting agonist protocol **Arm 2:** short acting agonist protocol
Outcomes	Clinical pregnancy; oocyte number
Starting date	Registered on 6 February 2019 Status: recruiting as of 19 March 2022 (last updated on 11 F bruary 019
Contact information	gongyan_496181657@qq.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR19 0021266

ChiCTR2000030356 2019

Study name	The effect of modified progestin primed o arian stimulation program in whole embryo freezing cycle in the treatment of infertile patients: a ra domized controlled trial
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <40 ye rs; AFC 1 and >9; baseline FSH <12 IU/l; FET cycles only **Exclusion:** uterine anomaly abno mal karyotype; preimplantation genetic testing; recurrent pregnancy loss; basal oestrad ol lev l >80 pg/mL; functional cyst on day 2 of menstruation; donor cycle; systemic diseases
Interventions	**Arm 1:** GnRH antago ist **Arm 2:** MPA
Outcomes	Live bi th
Starting date	R gistered on 29 February 2020 Status: cruiting as of 19 March 2022 (last updated on 2 March 2020)
Contact information	caihe@bjmu.edu.cn
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000030356

ChiCTR2000041408 2 20

Study name	Efficacy and safety of letrozole combined with gonadotropin in ovulation induction in elderly patients with poor ovarian reserve: a multicenter, prospective, non-blind, randomized controlled clinical trial
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 40-45 years; low ovarian reserve; AFC <5; AMH ≥0.1 and <1.2 ng/ml; first four cycles of ART

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ChiCTR2000041408 2020 *(Continued)*

	Exclusion criteria: previous participation in the trial; unilateral or bilateral hydrosalpinges; uterine abnormality; abnormal karyotype; male partner with low spermatogenesis, non-obstructive azoospermia or AZF gene microdeletion; allergy to letrozole or gonadotrophins; contraindications to ART or pregnancy
Interventions	**Arm 1:** letrozole plus conventional dose of gonadotrophin **Arm 2:** GnRH antagonist protocol
Outcomes	Clinical pregnancy; oocyte number; miscarriage; live birth
Starting date	Registered on 25 December 2020 Status: recruiting as of 19 March 2022 (last updated on 15 March 2021)
Contact information	zhaoxmiao@163.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR20000 1408

ChiCTR2100043606 2021

Study name	The effect of recombinant Luteinizing Hormone (LH) supplementation in controlled ovarian hyperstimulation outcome in women with low LH ncentration during mid- and late-follicular phase: a single-centre, prospective, random ed controlled study
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-3 years; normal uterus **Exclusion criteria:** repeat d implantation failure; endocrine disorders; PCOS; systemic disease; contraindication to pregnancy or gonadotrophins; blood borne viruses
Interventions	**Arm 1:** rFSH **Arm 2:** rFSH plus rLH
Outcomes	Oo yte number; clinical pregnancy; ongoing pregnancy; OHSS
Starting date	Reg te ed on 23 February 2021 Status: recruiting as of 19 March 2022 (last updated on 22 June 2021)
Contact information	tangsisley@163.com
Notes	ttps://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2100043606

ChiCTR2100044921 2021

Study name	Comparison of endometrial receptivity between GnRH-antagonist protocol and GnRH-agonist protocol in normal ovarian responders: a randomized controlled trial
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-<38 years; AFC >6; FSH <10 IU/l; AMH >1.11 ng/ml; BMI 18-29 kg/m^2

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ChiCTR2100044921 2021 *(Continued)*

	Exclusion criteria: serious factors affecting embryo implantation (hydrosalpinx, adenomyosis, adhesions, uterine malformations, endometriosis grade III and IV; PCOS; RIF; endometrial pathology; alcoholism, tumours, mental disorders
Interventions	**Arm 1:** GnRH antagonist protocol **Arm 2:** long GnRH agonist protocol
Outcomes	Clinical pregnancy; oocyte number
Starting date	Registered on 31 March 2021 Status: recruiting as of 19 March 2022 (last updated on 2 N vembe 202)
Contact information	liushine2006@163.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR21 0044921

ChiCTR-IOR-16009349 2016

Study name	Comparison of the clinical outcomes for normo-ovulatory patients undergoing IVF procedure using mid-late follicular phase stimulation vs Utrogestan protocol
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-40 years no mal menstrual cycles (25-35 days), tubal or male factor; baseline FSH <10 IU/l, AFC >4 **Exclusion criteria:** PCOS endometriosis grade 3 or higher; documented ovarian failure; contraindications to ovarian s mulation treatment
Interventions	**Arm 1:** mid-late foll ular start of hMG **Arm 2:** Utroges n® and MG
Outcomes	Oocyte numb r
Starting date	R gistered on 8 October 2016 Status: pending" as of 19 March 2022 (last updated on 18 April 2017)
Contact information	fuyonglunivf@163.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-IOR-16009349

ChiCTR-IPR-1400567 2014

Study name	A comparison of outcomes from ART cycles stimulated with recombinant follicle stimulating hormone and highly purified human menopausal gonadotropin
Methods	Randomised controlled trial.
Participants	**Inclusion criteria:** age 20-38 years; AFC >8; baseline FSH <10 mIU/ml; first IVf cycle; long agonist protocol

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ChiCTR-IPR-14005678 2014 *(Continued)*

	Exclusion criteria: endometriosis; adenomyosis; uterine anomalies; contraindications to ART/ pregnancy
Interventions	**Arm 1:** rFSH **Arm 2:** hMG
Outcomes	Clinical pregnancy; oocyte number; cancellation
Starting date	Registered on 7 August 2014 Status: recruiting as of 19 March 2022 (last updated on 18 April 2017)
Contact information	shijuanzi@126.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-I R-14005678

ChiCTR-IPR-15006380 2015

Study name	The clinical outcome of two ovarian stimulation protocols without prolonged pituitary down-regulation for endometriosis patients undergo ng IVF/ICSI cycles
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 25-40 yea ; regular ovulation; FSH <10 IU/l; AFC 5-15 **Exclusion criteria:** ovarian fa ur ; PCOS; acute genital tract infection; other systemic conditions
Interventions	**Arm 1:** hMG plus MPA in e foll ular phase **Arm 2:** short GnRH-a (formu tion unspecified)
Outcomes	Oocyte number numbe of cleavage-stage embryos
Starting date	Registered on 6 April 2015 Sta us: re ruiting as of 19 March 2022 (last updated on 18 April 2017)
Contact information	kua gy np@126.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-IPR-15006380

ChiCTR-IPR-160083 5 2016

Study name	Comparison of Different Gonadotropins in PCOS Patients undergoing in vitro Fertilization: A Randomized Controlled Trial
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-37 years; PCOS; first IVF cycle; baseline FSH ≤12 IU/l **Exclusion criteria:** ovarian surgery; allergy to FSH or LH; abnormal hysterosalpingography; other endocrine disease; severe endometriosis; hypothalamic or pituitary tumours; malignant neoplasm in ovary, uterus or breast; participation in other clinical trials within three months before enrolment; drug or alcohol dependence; infection or other contraindications to IVF/ICSI-ET

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ChiCTR-IPR-16008355 2016 *(Continued)*

Interventions	**Arm 1:** rFSH **Arm 2:** hMG
Outcomes	Oocyte number
Starting date	Registered on 24 April 2016 Status: recruiting as of 19 March 2022 (last updated on 18 April 2017)
Contact information	kilody@foxmail.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-IPR-1 008355

ChiCTR-IPR-17012964 2017

Study name	The effect of clomiphene citrate on clinical o tcome in P ogestin-Primed Ovarian Stimulation in women with polycystic ovarian syndrome und rgoing IV cycle
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-38 years; PCOS (Ro terdam criteria); FSH <10 IU/l; BMI <25 kg/m^2 **Exclusion criteria:** male factor, ovarian fa ure, severe endometriosis, acute genital tract infection and other systemic diseases
Interventions	**Arm 1:** hMG and dydrogesteron **Arm 2:** clomifene plus hMG and dydrogesterone
Outcomes	Oocyte number
Starting date	Registered on 1 Octobe 2017 Status: rec u ting as of 19 March 2022 (last updated on 16 October 2017)
Contact information	kuangyanp@126.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-IPR-17012964

ChiCTR-IPR-17012998 2017

Study name	he clinical outcomes of MPA and Duphaston and Utrogestan in Primed-progesterone ovarian stimulation protocol for patients with polycystic ovarian syndrome undergoing IVF cycle
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-38 years; PCOS (Rotterdam criteria); FSH <10 IU/l; BMI <25 kg/m^2 **Exclusion criteria:** male factor; ovarian failure; severe endometriosis; acute genital tract infection; other systemic conditions
Interventions	**Arm 1:** hMG and MPA **Arm 2:** hMG and dydrogesterone

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ChiCTR-IPR-17012998 2017 *(Continued)*

	Arm 3: hMG and Utrogestan®
Outcomes	Oocyte number; clinical pregnancy
Starting date	Registered on 16 October 2017 Status: recruiting as of 19 March 2022 (last updated on 23 October 2017)
Contact information	kuangyanp@126.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-IPR-1701299

ChiCTR-TRC-14004965 2014

Study name	A prospective, randomized, controlled trial of rec binant FSH combined with HP-HMG on ovarian response and clinical outcomes
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-38 years; AFC >7; baseline FSH <10 mIU/ml; first ART cycle; luteal phase agonist long protocol **Exclusion criteria:** endometriosis; ade omy is; uterine abnormalities; contraindications to ART
Interventions	**Arm 1:** rFSH **Arm 2:** rFSH and hMG
Outcomes	Clinical pregnancy; live b rth; oocyte number
Starting date	Registered on 22 June 2014 Status: recruiting as f 1 March 2022 (last updated on 18 April 2017)
Contact information	shijuanzi@126.com
Notes	https://tr lsearch who.int/Trial2.aspx?TrialID=ChiCTR-TRC-14004965

EUCTR2015-003779-31-ES 2015

Study name	Pr spective, Randomized Open Trial to Evaluate the Efficacy of Highly Purified Urinary FSH (Fos- ipur®, IBSA) versus Recombinant FSH (Bemfola® Finox) in Oocyte Donors Undergoing Controlled Ovarian Stimulation Based on Receptor N680S FSH Gene Polymorphism
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-30 years; BMI >18 and <28 kg/m^2; AFC >9 and <25; presence of both ovaries **Exclusion criteria:** concurrent participation in another study
Interventions	**Arm 1:** uFSH **Arm 2:** rFSH

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EUCTR2015-003779-31-ES 2015 *(Continued)*

Outcomes	Oocyte number
Starting date	Registered on 30 October 2015 Status: "ongoing" as per trial web site
Contact information	montsevidal@crossdata.es
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2015-003779-31-ES https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudra t_number:2015-003779-31

EUCTR2017-002783-40-AT 2018

Study name	A trial to compare the efficacy and safety of indi du lised F 999049 (follitropin delta) dosing in women undergoing controlled ovarian stimulation
Methods	Randomised controlled trial
Participants	Full list of inclusion and exclusion criteria available at trial registry entry
Interventions	**Arm 1:** short GnRH antagonist plus rFSH **Arm 2:** long GnRH agonist plus rFSH
Outcomes	Oocyte number; clinical pregnanc ; on oing pregnancy; OHSS
Starting date	Registered on 19 November 2 18 Status: ongoing as per trial web site on 19 March 2022 (last updated on 8 June 2020)
Contact information	DK0-Disclosure@ferr g.com
Notes	https://trials arch who int/Trial2.aspx?TrialID=EUCTR2017-002783-40-AT http //www.cl icaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-002783-40

IRCT20080831001141N33 2021

Study name	Comparison of Ovarian Stimulation Cycle Outcome in Medroxy Progesterone Acetate and Gonadotropin Protocol with Antagonist and Gonadotropin Protocol in Polycystic Ovarian Syndrome atients Undergoing In-Vitro fertilization/ Intracytoplasmic Sperm Injection (IVF/ICSI)
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-39 years; BMI <30 kg/m^2 **Exclusion criteria:** systemic disease; endometriosis grade 3 or higher; hormonal treatment within the past three months; contraindications to ovarian stimulation; surgical sperm retrieval
Interventions	**Arm 1:** MPA plus rFSH with or without hMG **Arm 2:** short GnRH antagonist plus rFSH with or without hMG

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IRCT20080831001141N33 2021 *(Continued)*

Outcomes	Clinical pregnancy; OHSS
Starting date	Registered on 1 January 2021 Status: recruiting as of 19 March 2022 (updated on 22 February 2021)
Contact information	mostafaeip@yahoo.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20080831001141N33

IRCT20120104008611N12 2021

Study name	Comparison the effect of combining letrozole and gonadotropin with gonadotropin alone on the IVF / ICSI cycle success rate in women with endometriosis
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-35 years; BMI <30 kg/ ^{2}; first ART cycle; no uterine malformations; sperm motility ≥20%; AMH >1 ng/ml **Exclusion criteria:** letrozole or clomifene c trate for ovulation induction
Interventions	**Arm 1:** short GnRH agonist plus letrozole and hMG **Arm 2:** short GnRH agonist plus hM
Outcomes	Oocyte number; clinical pregna cy
Starting date	Registered on 19 March 2021 Status: "complete" as of 19 March 2022 (updated on 12 July 2021)
Contact information	pakniat110@ya oo com
Notes	https://trials arch.who.int/Trial2.aspx?TrialID=IRCT20120104008611N12 Authors c ntacted on 19 March 2022 requesting outcome data

IRCT20180528039878N2 2021

Study name	Comparison of pregnancy outcome between flexible progestin primed ovarian stimulation and gonadotropin releasing hormone GnRH antagonist protocol in patients with polycystic ovarian syndrome-Randomized clinical trial
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <41 years; PCOS (Rotterdam criteria) **Exclusion criteria:** moderate and severe endometriosis; contraindications to MPA; allergy to MPA; severe male factor
Interventions	**Arm 1:** MPA plus gonadotrophins (unspecified) **Arm 2:** short GnRH antagonist plus gonadotrophins (unspecified)

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IRCT20180528039878N2 2021 *(Continued)*

Outcomes	Clinical pregnancy; ongoing pregnancy; OHSS
Starting date	Registered on 6 April 2021 Status: "pending" as of 19 March 2022 (last updated on 26 April 2021)
Contact information	marzieh.mehrafza@gmail.com
Notes	https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20180528039878N2

IRCT20210405050852N1 2021

Study name	Comparison of luteal phase stimulation with follicular p ase stimulation in poor ovarian response
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <40 years; regular me strual cycle ; normal uterus on ultrasound and HSG; AMH <1.1 ng/ml or AFC <5
Interventions	**Arm 1:** MPA plus GnRH antagonist and FSH **Arm 2:** short GnRH antagonist plus FS plus hMG
Outcomes	Clinical pregnancy
Starting date	Registered on 10 June 2021 Status: "pending" as of 19 Ma ch 2022 (last updated on 21 June 2021)
Contact information	vahabi.mozhgan@yahoo com
Notes	https://trialsear h.who.int/Trial2.aspx?TrialID=IRCT20210405050852N1

NCT02912988 2016

Study name	Letro le in Stimulated IVF Cycles
Methods	Randomised controlled trial
Participants	**In lusion criteria:** age <42 years; AFC ≥3 **xclusion criteria:** donor oocyte treatment; preimplantation genetic diagnosis; uterine anomalies on HSG or saline infusion sonography; untreated hydrosalpinges; previous low response.
Interventions	**Arm 1:** short GnRH antagonist plus letrozole and hMG/FSH **Arm 2:** short GnR antagonist plus hMG/FSH
Outcomes	Live birth; miscarriage; clinical pregnancy; ongoing pregnancy; OHSS; oocyte number
Starting date	Registered on 23 September 2016 Status: recruiting as of 19 March 2022 (last updated on 29 April 2021)

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NCT02912988 2016 *(Continued)*

Contact information	nghye@hku.hk
Notes	https://clinicaltrials.gov/ct2/show/NCT02912988

NCT03809429 2019

Study name	Follitropin Delta in Long GnRH Agonist and GnRH Antagonist Protocols (BEYOND)
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18-40 years; first ART cycle; tubal, endom triosis o male infertility; regular menstrual cycles; BMI 17.5-32 kg/m^2 **Exclusion criteria:** very high ovarian reserve (undefined); severe endometriosis; history of repeated miscarriage; chromosomal abnormalities in one of he par ners; thrombophilia; chronic disease
Interventions	**Arm 1:** GnRH agonist plus rFSH (timing of agonist unstated) **Arm 2:** GnRH antagonist plus rFSH
Outcomes	Oocyte number; cancellation; clinical pregnancy; ongoing pregnancy; OHSS
Starting date	Registered on 18 January 2019 Status: "completed" as of 19 March 022 (updated on 23 February 2022) No results found
Contact information	Not found
Notes	https://clinicaltrials.gov/ct2/ how/NCT03809429

NCT04268927 2020

Study name	E tended Letrozole Regimen Co-treatment With Gonadotropin Releasing Hormone Antagonist Protocol V rsus Gonadotropin Releasing Hormone Antagonist Protocol in Poor Responders Undergoing IVF-ET
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 30-42 years; low ovarian response (Bologna) **xclusion criteria:** age >42 years; FSH >12 IU/l; irregular menstrual cycles; unilateral PCOS; endometriosis; male factor infertility requiring ICSI; recurrent miscarriage; endocrine pathology; systemic disease contraindicating pregnancy
Interventions	**Arm 1:** short GnRH antagonist plus letrozole and uFSH **Arm 2:** short GnRH antagonist plus uFSH
Outcomes	Oocyte number
Starting date	Registered on 13 February 2020 Status: "unknown" as of 22 April 2022

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NCT04268927 2020 *(Continued)*

	No results found
Contact information	umfrfouda@yahoo.com
Notes	https://clinicaltrials.gov/ct2/show/NCT04268927

NCT04356105 2020

Study name	Protocols of IVF/ICSI in Poor Responders
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 30-43 years; low ovarian respons **Exclusion criteria:** age >43 years; baseline FSH >1 mIU/m ; previous ovarian surgery; ovarian endometrioma; uterine anomalies; medical diso ders; hor onal disorders; BMI >30 kg/m^2; severe male factor
Interventions	**Arm 1:** short GnRH antagonist plus letrozole and rF H **Arm 2:** short GnRH agonist flare plus rFSH
Outcomes	Oocyte number; number of embryos cryopres ved; clinical pregnancy; miscarriage; ongoing pregnancy; live birth; cancellation
Starting date	Registered on 22 April 2020 Status: "completed" as of 19 Marc 022 (last updated on 16 November 2021)
Contact information	No email contact found
Notes	Results awaited

NCT04414748 2020

Study name	Co pa son of the Euploid Rate of Blastocyst Between PPOS and GnRH Antagonist Protocol in Patients U dergoing PGT-A
Methods	Randomised controlled trial
Participants	**Incl sion criteria:** age 20-43 years; AFC ≥5 on day 2-5 of the menstrual cycle; preimplantation genetic testing for aneuploidy for advanced maternal age, recurrent miscarriage and RIF **Exclusion criteria:** functional ovarian cyst with serum oestradiol >100 pg/ml; recipient of oocyte donation; untreated hydrosalpinx or endometrial polyp
Interventions	**Arm 1:** short GnRH antagonist (gonadotrophin unstated) **Arm 2:** dydrogesterone (gonadotrophin unstated)
Outcomes	Blastocyst number; clinical pregnancy; ongoing pregnancy; live birth; multiple pregnancy; ectopic pregnancy; miscarriage
Starting date	Registered on 4 June 2020

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NCT04414748 2020 *(Continued)*

	Status: recruiting as of 19 March 2022 (last updated on 7 July 2020)
Contact information	lihe198900@163.com
Notes	https://clinicaltrials.gov/ct2/show/NCT04414748

NCT04414761 2020

Study name	Live Birth Rate Between PPOS and GnRH Antagonist Protocol in Patie ts With Anticipated High Ovarian Response
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-43 years; first ART cycle; AFC > 5 on day 2-5 of menstrual cycle **Exclusion criteria:** function ovarian cyst with serum oestradiol >100 pg/ml; recipient of oocyte donation; preimplantation genetic testing; untr ated hydro alpinx or endometrial polyp
Interventions	**Arm 1:** short GnRh antagonist (gonadotrophins un ed) **Arm 2:** MPA (gonadotrophins unstated)
Outcomes	Live birth; clinical pregnancy; ongoing pregn cy; oocyte number; blastocyst number; multiple pregnancy; ectopic pregnancy; misc rriage
Starting date	Registered on 4 June 2020 Status: recruiting as of 19 March 2022 (last updated on 18 March 2021)
Contact information	lihe198900@163.com
Notes	https://clinicaltrials gov/ct2/show/NCT04414761

NCT04487925 2020

Study name	Co trol ed Ovarian Stimulation Versus Modified Natural Cycles in Poor Responders (MONACO)
Methods	Randomised controlled trial
Participants	**nclusion criteria:** age 18 to 44 years; BMI 18.5-35 kg/m^2; regular menstrual cycles (between 21 and 35 days); two ovaries present; low ovarian response (POSEIDON groups 3 and 4) **xclusion criteria:** untreated and uncontrolled thyroid dysfunction; tumours of the ovary, breast, uterus, pituitary or hypothalamus; ovarian cysts or enlarged ovaries; malformations of the reproductive organs; current use of oral contraceptives, antipsychotics, antiepileptics or chemotherapy; previous antibiotic hypersensitivity reactions; planned PGT
Interventions	**Arm 1:** modified natural cycle with rFSH **Arm 2:** short GnRH antagonist plus rFSH
Outcomes	Ongoing pregnancy
Starting date	Registered on 27 July 2020

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NCT04487925 2020 *(Continued)*

	Status: not yet recruiting as of 19 March 2022 (last updated on 1 February 2022)
Contact information	studieco.vrouwenkliniek@uzgent.be
Notes	https://clinicaltrials.gov/ct2/show/NCT04487925

NCT04537078 2020

Study name	Progestin Primed Double Stimulation Protocol Versus Flexible GnRH Antagonist Protocol in Poor Responders
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-45 years; low ovarian respons defined by the Bologna criteria **Exclusion criteria:** male factor infertility due o azoosp rmia; uncorrected uterine pathology; severe endometriosis; BMI >35 kg/m^2
Interventions	**Arm 1:** dydrogesterone plus gonadotrophins (unsp ified) **Arm 2:** short GnRH antagonist plus gonad trophins (unspecified)
Outcomes	Embryo number; clinical pregnancy; ongoing pregnancy
Starting date	Registered on 3 September 2020 Status: completed as of 19 Ma ch 2022 (last updated on 17 February 2022)
Contact information	No email contact availab
Notes	https://clinicaltrials.gov/c / how/NCT04537078

NCT04539067 2020

Study name	Ef ect of Controlled Ovarian Stimulation in Quality of Oocyte and Embryo
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 20-35 years; normal uterus and ovaries; unexplained infertility; no endometriosis **Exclusion criteria:** low response to gonadotrophins; prior history of >3 unsuccessful ICSI cycles; anatomical malformations in the reproductive system
Interventions	**Arm 1:** hMG only (downregulation unstated) **Arm 2:** uFSH plus hMG (downregulation unstated)
Outcomes	Oocyte number; embryo number
Starting date	Registered on 4 September 2020 Status: "not yet recruiting" as of 19 March 2022 (last updated on 4 September 2020)

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NCT04539067 2020 *(Continued)*

Contact information	marwatarahony9@gmail.com
Notes	https://clinicaltrials.gov/ct2/show/NCT04539067

NCT04654741 2020

Study name	The Rate of Embryo Euploidy in Progestin-primed Ovarian Stimulation Cycles (PPOS)
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18 to 40 years; recurrent miscarriage; RIF; severe m le factor **Exclusion criteria:** ovarian cysts; previous surgery; abnormal ka yotype; genetic or systemic disease
Interventions	**Arm 1:** MPA priming (gonadotrophin unstate) **Arm 2:** short GnRH antagonist (gonadotrophin unstated)
Outcomes	Oocyte number
Starting date	Registered on 4 December 2020 Status: recruiting as of 19 March 2022 (l st pdated on 4 December 2020)
Contact information	ergreco1@virgilio.it
Notes	https://clinicaltrials.gov/ct2/s ow/NCT04654741

NCT04719000 2021

Study name	PErsonalized Addition of Recombinant LH in Ovarian Stimulation (PEARL)
Methods	Ra domised controlled trial
Participants	**Inclu on criteria:** age 35-40 years; AFC ≥5 and/or AMH ≥1.2 ng/ml; previous low ovarian response on GnRH ntagonist protocol **Exclusion criteria:** low ovarian response; PCOS; AFC >20; uterine anomalies; untreated hydros- lpinx; PGT-A; surgical sperm retrieval
Interventions	**Arm 1:** short GnRH antagonist plus rFSH and rLH **Arm 2:** short GnRH antagonist plus rFSH only
Outcomes	Oocyte number
Starting date	Registered on 22 January 2021 Status: recruiting as of 19 March 2022 (last updated on 22 February 2022)
Contact information	nikpol@dexeus.com, nacrod@dexeus.com
Notes	https://clinicaltrials.gov/ct2/show/NCT04719000

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NCT04728659 2021

Study name	Desogestrel Versus GnRH Antagonist in IVF/ICSI (DEGOS)
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age 18 to 42 years; regular menstrual cycles (25-35 days); baseline serum FSH up to 10 IU/l **Exclusion criteria:** ovarian failure; basal FSH >10 IU/l; no antral foll cles by ultrasound examination; PCOS; contraindications to ART
Interventions	**Arm 1:** desogestrel plus gonadotrophin (unstated) **Arm 2:** short GnRH antagonist plus gonadotrophin (unstated)
Outcomes	Oocyte number; cancellation; embryo number
Starting date	Registered on 28 January 2021 Status: recruiting as of 19 March 2022 (last upda d on 28 January 2021)
Contact information	ergreco1@virgilio.it
Notes	https://clinicaltrials.gov/ct2/show/NCT 47286 9

NCT04983173 2021

Study name	INTEnsity of ovariaN Stim lation nd Embryo Quality (INTENS-EQ)
Methods	Randomised controlled trial
Participants	**Inclusion criter a:** age 3 to 40 years; AFC 5-10; AMH up to 1.5 ng/ml; BMI 18.5-25 kg/m^2 **Exclusion c teria:** AFC >10; untreated autoimmune, endocrine or metabolic disorders; contraindicati n fo hormonal treatment; preimplantation genetic diagnosis cycles; severe male factor; recent histo y of severe disease requiring regular treatment
Interventions	**Arm 1:** hort GnRH antagonist plus clomifene citrate and rFSH **Arm 2:** short GnRH antagonist plus rFSH
Outcomes	Blastocyst number; oocyte number; cancellation; clinical pregnancy; ongoing pregnancy; OHSS; miscarriage
Starting date	Registered on 30 July 2021 Status: recruiting as of 19 March 2022 (last updated on 11 January 2022)
Contact information	nacrod@dexeus.com, nikpol@dexeus.com
Notes	NCT04983173

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NCT04989348 2021	
Study name	Euploid Rate of Blastocyst Derived From PPOS VS Antagonist Protocol
Methods	Randomised controlled trial
Participants	**Inclusion criteria:** age <43 years; PGT-A **Exclusion criteria:** functional ovarian cyst with serum oestradiol >100 pg/ml; use of donor gametes; untreated hydrosalpinx or endometrial polyp; moderate or severe endometriosis
Interventions	**Arm 1:** short GnRH antagonist (gonadotrophins unstated) **Arm 2:** MPA or dydrogesterone (gonadotrophins unstated)
Outcomes	Clinical pregnancy; ongoing pregnancy; live birth
Starting date	Registered on 4 August 2021 Status: not yet recruiting as of 19 March 2022 (ast upda ed on 4 August 2021)
Contact information	ptchen1@hotmail.com
Notes	https://clinicaltrials.gov/ct2/show/NCT04989348

AFC, antral follicle count; AMH, anti-Müllerian hormone; ART, assisted rep odu t e technology; BMI, body mass index; COS, controlled ovarian stimulation; FET, frozen embryo transfer; FSH, follicle stimul ting ormone; GnRH, gonadotrophin-releasing hormone; hMG, human menopausal gonadotrophin; HSG, hysterosalpingography; ICSI intracytoplasmic sperm injection; IVF, in vitro fertilisation; LH, luteinising hormone; MPA, medroxyprogesterone acetate; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome; PGT, preimplantation genetic testing; PGT-A, preimplantation gene ic esting for aneuploidy; PPOS, progestin-primed ovarian stimulation; rFSH, recombinant follicle-stimulating hormone; RIF, recurrent impla t ion failure

DATA AND ANALYSES

Comparison 1. Direct comparison: Short GnRH antagonist versus long GnRH agonist protocols

Outcome or subgroup title	No. of stu ies	No of partici-pants	Statistical method	Effect size
1.1 Live birth	6	2043	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.85, 1.12]
1.1.1 Normal response	6	2043	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.85, 1.12]
1.2 OHSS		2246	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 0.99]
1.2.1 Normal response	5	1890	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 0.99]
1.2.2 High respons	2	356	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.33, 2.41]
1.3 Clinical pregnancy	12	2958	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.79, 0.99]
1.3.1 Normal response	8	1583	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
1.3.2 High response	1	220	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.68, 1.07]
1.3.3 Low response	3	1155	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.71, 1.24]

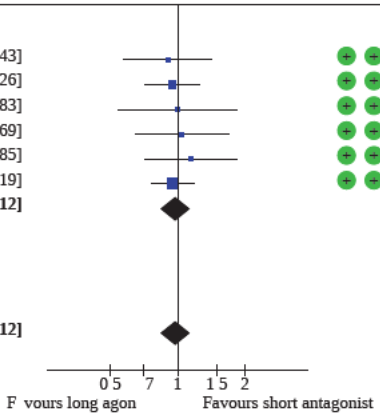
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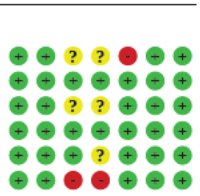
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Ongoing pregnancy	13	4065	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]
1.4.1 Normal response	5	1987	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.07]
1.4.2 High response	3	576	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.77, 1.15]
1.4.3 Low response	5	1502	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.67, 1.16]
1.5 Multiple pregnancy	4	1195	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.53, 1.32]
1.5.1 Normal response	2	501	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.51, 1.65]
1.5.2 High response	1	300	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.38, 2.15]
1.5.3 Low response	1	394	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.11, 1.67]
1.6 Miscarriage	13	3911	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.22]
1.6.1 Normal response	8	2400	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.73, 1.24]
1.6.2 High response	2	356	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.44, 1.76]
1.6.3 Low response	3	1155	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.60, 2.23]
1.7 Ectopic	4	541	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.27, 8.73]
1.7.1 Normal response	3	475	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.14, 9.20]
1.7.2 Low response	1	66	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 71.07]
1.8 Cancellation	18	4832	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.67, 1.55]
1.8.1 Normal response	10	2754	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.21]
1.8.2 High response	3	576	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.76, 2.66]
1.8.3 Low response	5	1502	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.05, 3.23]
1.9 Oocyte number	23	5238	Mean Difference (IV, Random, 95% CI)	-0.85 [-1.52, -0.18]
1.9.1 Normal response	15	3302	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.75, 0.33]
1.9.2 High response	3	434	Mean Difference (IV, Random, 95% CI)	-0.08 [-1.58, 1.41]
1.9.3 Low response	5	1502	Mean Difference (IV, Random, 95% CI)	-1.24 [-2.02, -0.46]
1.10 Frozen embryo number	6	2098	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.32, -0.02]
1.10.1 Normal response	5	2032	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.33, 0.01]
1.10.2 Low response	1	66	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.79, 0.11]

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Analysis 1.1. Comparison 1: Direct comparison: Short GnRH antagonist versus long GnRH agonist protocols, Outcome 1: Live birth

Study or Subgroup	Short antagonist Events	Short antagonist Total	Long agonist Events	Long agonist Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Normal response						
Albano 2000	42	188	21	85	9 7%	0 90 [0 57 , 1 43]
Garcia-Velasco 2011	51	115	53	113	25 1%	0 95 [0 71 , 1 26]
Huirne 2006	17	91	17	91	5 5%	1 00 [0 55 , 1 83]
Lin 2006	22	60	21	60	8 8%	1 05 [0 65 , 1 69]
Papanikolaou 2012	27	96	23	94	8 8%	1 15 [0 71 , 1 85]
Toftager 2016	122	534	123	516	42 0%	0 96 [0 77 , 1 19]
Subtotal (95% CI)		**1084**		**959**	**100.0%**	**0.98 [0.85 , 1.12]**
Total events:	281		258			
Heterogeneity: Tau² = 0 00; Chi² = 0 72, df = 5 (P = 0 98); I² = 0%						
Test for overall effect: Z = 0 35 (P = 0 73)						
Total (95% CI)		**1084**		**959**	**100.0%**	**0.98 [0.85 , 1.12]**
Total events:	281		258			
Heterogeneity: Tau² = 0 00; Chi² = 0 72, df = 5 (P = 0 98); I² = 0%						
Test for overall effect: Z = 0 35 (P = 0 73)						
Test for subgroup differences: Not applicable						

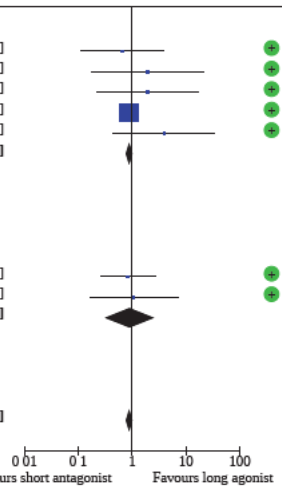




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparis n 1: Direct comparison: Short GnRH antagonist versus long GnRH agonist protocols, Outcome 2: OHSS

Study or Subgroup	Short antagonis Events	Short antagonis T al	ong agonist E ent	ong agonist Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Normal response						
Huirne 2006		9	3	91	0 4%	0 67 [0 11 , 3 90]
Papanikolaou 2012		96	1	94	0 2%	1 96 [0 18 , 21 23]
The European and Middle East Ogalutran Group 2001	4	226	1	111	0 3%	1 96 [0 22 , 17 37]
Toftager 2016	252		279	516	97 3%	0 87 [0 77 , 0 98]
Xavier 2005	4	66	1	65	0 3%	3 94 [0 45 , 34 31]
Subtotal (95% CI)		**1013**		**877**	**98.6%**	**0.88 [0.78 , 0.99]**
Total events	264		285			
Heterogeneity Tau² = 0 00; Chi² = 2 95, df = 4 (P = 0 57); I² = 0%						
Test for overall effect Z = 2 11 (P = 0 03)						
1.2.2 High response						
Haydardedeoglu 2012	5	150	6	150	1 0%	0 83 [0 26 , 2 67]
Hwang 2004	2	27	2	29	0 4%	1 07 [0 16 , 7 10]
Subtotal (95% CI)		**177**		**179**	**1.4%**	**0.89 [0.33 , 2.41]**
Total events	7		8			
Heterogeneity Tau² = 0 00 hi² = 0 05 f = 1 (P = 0 2); I² = 0%						
Test for overall effect Z 22 (P = 0 82)						
Total (95% CI)		**1190**		**1056**	**100.0%**	**0.88 [0.78 , 0.99]**
Total events	271		293			
Heterogeneity Tau² = 0 00; C = 3 00, df = 6 (P = 0 81); I² = 0%						
Test for overall effect Z = 2 12 (P 03)						
Test for subgroup differences Chi² = 0 00, df = 1 (P = 0 98), I² = 0%						



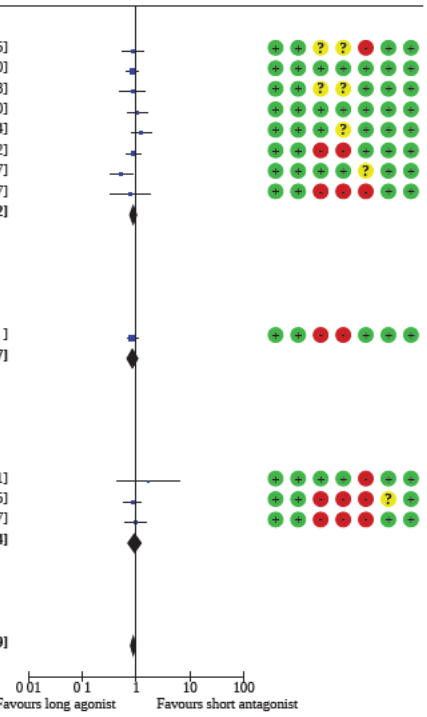


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 1.3. Comparison 1: Direct comparison: Short GnRH antagonist versus long GnRH agonist protocols, Outcome 3: Clinical pregnancy

Study or Subgroup	Short antagonist Events	Short antagonist Total	Long agonist Events	Long agonist Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Normal response						
Albano 2000	42	188	22	85	6 0%	0 86 [0 55 , 1 35]
Garcia-Velasco 2011	56	115	64	113	19 7%	0 86 [0 67 , 1 10]
Huirne 2006	19	91	22	91	4 1%	0 86 [0 50 , 1 48]
Lin 2006	25	60	24	60	6 5%	1 04 [0 68 , 1 60]
Papanikolaou 2012	32	96	25	94	6 3%	1 25 [0 81 , 1 94]
The European and Middle East Ogalutran Group 2001	73	226	40	111	12 4%	0 90 [0 66 , 1 22]
Verpoest 2017	16	60	31	62	5 1%	0 53 [0 33 , 0 87]
Xavier 2005	8	66	10	65	1 6%	0 79 [0 33 , 1 87]
Subtotal (95% CI)		**902**		**681**	**61.8%**	**0.88 [0.76 , 1.02]**
Total events	271		238			
Heterogeneity Tau² = 0 00; Chi² = 7 25, df = 7 (P = 0 40); I² = 3%						
Test for overall effect Z = 1 71 (P = 0 09)						
1.3.2 High response						
Basly 2012	58	110	68	110	22 8%	0 85 [0]
Subtotal (95% CI)		**110**		**110**	**22.8%**	**0.8 [0.68 , 1.07]**
Total events	58		68			
Heterogeneity Not applicable						
Test for overall effect Z = 1 36 (P = 0 18)						
1.3.3 Low response						
Cheung 2005	5	33	3	33	0 7%	1 67 [0 43 , 6 41]
Revelli 2014	47	355	52	340	9 0%	0 87 [0 60 , 1 25]
Youssef 2017	30	195	31	199	5 7%	0 99 [0 62 , 1 57]
Subtotal (95% CI)		**583**		**572**	**15.4%**	**93 [0.71 , 1.24]**
Total events	82		86			
Heterogeneity Tau² = 0 00; Chi² = 0 93, df = 2 (P = 0 63); I² = 0%						
Test for overall effect Z = 0 47 (P = 0 64)						
Total (95% CI)		**1595**		**13**	**100 %**	**0.88 [0.79 , 0.99]**
Total events	411		392			
Heterogeneity Tau² = 0 00; Chi² = 8 44, df = 11 (P = 0 67); I² = 0%						
Test for overall effect Z = 2 21 (P = 0 03)						
Test for subgroup differences Chi² = 0 25, df = 2 (P = 0 88), I² = 0%						

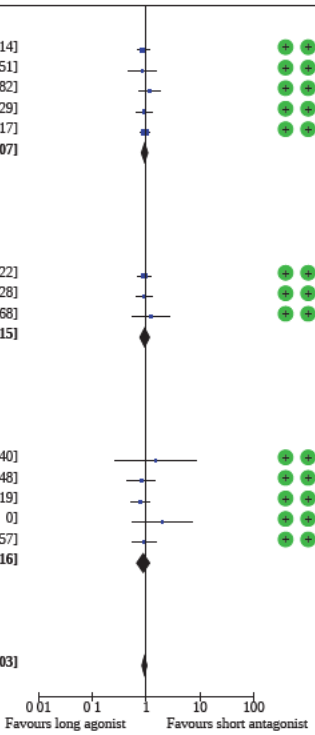


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 1.4. Comparison 1: Direct comparison: Short GnRH antagonist versus long GnRH agonist protocols, Outcome 4: Ongoing pregnancy

Study or Subgroup	Short antagonist Events	Total	Long agonist Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.4.1 Normal response							
Garcia-Velasco 2011	55	115	61	113	16 3%	0 89 [0 69 , 1 14]	+ + + - + + +
Huirne 2006	17	91	20	91	3 2%	0 85 [0 48 , 1 51]	+ + ? ? - + +
Papanikolaou 2012	28	96	24	94	4 9%	1 14 [0 72 , 1 82]	+ + + ? + + +
The European and Middle East Ogalutran Group 2001	70	226	37	111	9 9%	0 93 [0 67 , 1 29]	+ + - - + + +
Toftager 2016	133	534	135	516	24 9%	0 95 [0 77 , 1 17]	+ + - - + + +
Subtotal (95% CI)		**1062**		**925**	**59.3%**	**0.94 [0.82 , 1.07]**	
Total events	303		277				
Heterogeneity Tau² = 0 00; Chi² = 1 02, df = 4 (P = 0 91); I² = 0%							
Test for overall effect Z = 0 94 (P = 0 35)							
1.4.2 High response							
Basly 2012	52	110	56	110	14 7%	0 93 [0 71 , 1 22]	+ + - - + + +
Haydardedeoglu 2012	47	150	51	150	10 1%	0 92 [0 67 , 1 28]	+ + - - - - +
Hwang 2004	9	27	8	29	1 7%	1 21 [0 55 , 2 68]	+ + ? ? - + +
Subtotal (95% CI)		**287**		**289**	**26.4%**	**0.94 [0.77 , 1.15]**	
Total events	108		115				
Heterogeneity Tau² = 0 00; Chi² = 0 41, df = 2 (P = 0 82); I² = 0%							
Test for overall effect Z = 0 59 (P = 0 56)							
1.4.3 Low response							
Cheung 2005	3	33	2	33	0 4%	0 [0 27 , 8 40]	+ + + + - + +
Fusi 2020	17	136	21	137	3 0%	0 [0 45 , 1 48]	+ + - - ? + +
Revelli 2014	36	355	44	340	6 2%	0 78 [2 1 19]	+ + - - - ? +
Sunkara 2014	6	37	3	37	0 6%	2 00 [0 54 , 0]	+ + - + - + +
Youssef 2017	25	195	27	199	4 1%	0 94 [0 57 , 1 57]	+ + - - - + +
Subtotal (95% CI)		**756**		**746**	**14.3%**	**0.88 [0.67 , 1.16]**	
Total events	87		97				
Heterogeneity Tau² = 0 00; Chi² = 2 32, df = 4 (P = 0 68); I² = 0%							
Test for overall effect Z = 0 90 (P = 0 37)							
Total (95% CI)		**2105**		**1960**	**100.0%**	**0.93 [0.84 , 1.03]**	
Total events	498		489				
Heterogeneity Tau² = 0 00; Chi² = 3 91, df = 12 (P = 0 99); I² = 0%							
Test for overall effect Z = 1 36 (P = 0 17)							
Test for subgroup differences Chi² = 0 17, df = 2 (P = 0 92), I² = 0%							

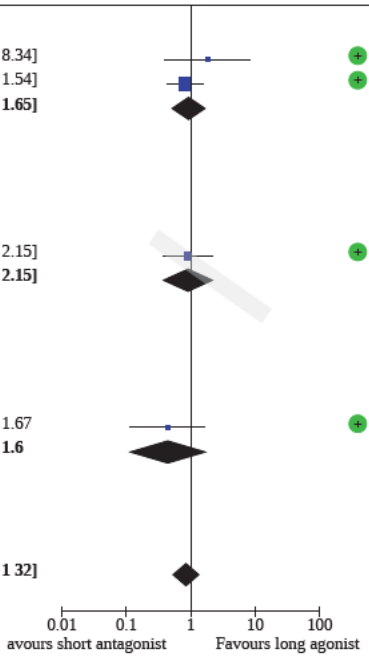


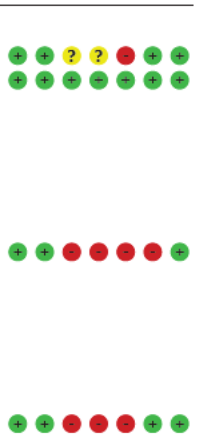
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 1.5. Comparison 1: Direct comparison: Short GnRH antagonist versus long GnRH agonist protocols, Outcome 5: Multiple pregnancy

Study or Subgroup	Short antagonist Events	Short antagonist Total	Long agonist Events	Long agonist Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Normal response						
Albano 2000	8	188	2	85	8.9%	1.81 [0.39 , 8.34]
Garcia-Velasco 2011	15	115	18	113	51.9%	0.82 [0.43 , 1.54]
Subtotal (95% CI)		**303**		**198**	**60.9%**	**0.92 [0.51 , 1.65]**
Total events:	23		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
1.5.2 High response						
Haydardedeoglu 2012	9	150	10	150	27.5%	0.90 [0.38 , 2.15]
Subtotal (95% CI)		**150**		**150**	**27.5%**	**0.90 [0.38 , 2.15]**
Total events:	9		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
1.5.3 Low response						
Youssef 2017	3	195	7	199	11.7%	0.44 [0.11 , 1.67
Subtotal (95% CI)		**195**		**199**	**11.7%**	**0.44 [0.11 , 1.6**
Total events:	3		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
Total (95% CI)		**648**		**547**	**100.0%**	**0.84 [0.53 , 1 32]**
Total events:	35		37			
Heterogeneity: Tau² = 0.00; Chi² = 1.91, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: Chi² = 1.03, df = 2 (P = 0.60), I² = 0%						



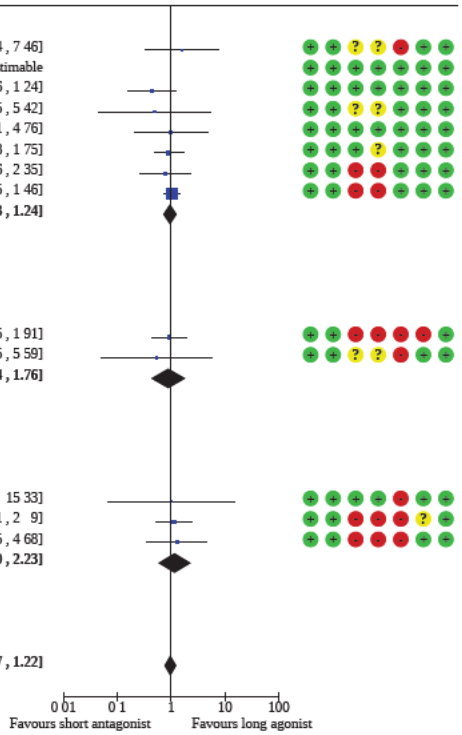


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 1.6. Comparison 1: Direct comparison: Short GnRH antagonist versus long GnRH agonist protocols, Outcome 6: Miscarriage

Study or Subgroup	Short antagonist Events	Total	Long agonist Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Normal response						
Albano 2000	7	188	2	85	2 2%	1 58 [0 34 , 7 46]
Franco 2003	0	14	0	6		Not estimable
Garcia-Velasco 2011	5	115	11	113	5 1%	0 45 [0 16 , 1 24]
Huirne 2006	1	91	2	91	0 9%	0 50 [0 05 , 5 42]
Lin 2006	3	60	3	60	2 2%	1 00 [0 21 , 4 76]
Papanikolaou 2012	15	96	16	94	12 9%	0 92 [0 48 , 1 75]
The European and Middle East Ogalutran Group 2001	8	226	5	111	4 5%	0 79 [0 26 , 2 35]
Toftager 2016	64	534	59	516	48 4%	1 05 [0 75 , 1 46]
Subtotal (95% CI)		**1324**		**1076**	**76.2%**	**0.95 [0.73 , 1.24]**
Total events	103		98			
Heterogeneity Tau² = 0 00; Chi² = 3 25, df = 6 (P = 0 78); I² = 0%						
Test for overall effect Z = 0 35 (P = 0 72)						
1.6.2 High response						
Haydardedeoglu 2012	13	150	14	150	10 3%	0 93 [0 45 , 1 91]
Hwang 2004	1	27	2	29	1 0%	0 54 [0 05 , 5 59]
Subtotal (95% CI)		**177**		**179**	**11.3%**	**0.89 [0.44 , 1.76]**
Total events	14		16			
Heterogeneity Tau² = 0 00; Chi² = 0 19, df = 1 (P = 0 66); I² = 0%						
Test for overall effect Z = 0 35 (P = 0 73)						
1.6.3 Low response						
Cheung 2005	1	33	1	33	0 7%	1 00 [15 33]
Revelli 2014	13	355	11	340	8 6%	1 13 [0 51 , 2 9]
Youssef 2017	5	195	4	199	3 2%	1 28 [0 35 , 4 68]
Subtotal (95% CI)		**583**		**572**	**12.5%**	**1.16 [0.60 , 2.23]**
Total events	19		16			
Heterogeneity Tau² = 0 00; Chi² = 0 04, df = 2 (P = 0 98); I² = 0%						
Test for overall effect Z = 0 44 (P = 0 66)						
Total (95% CI)		**2084**		**1827**	**100.0%**	**0.97 [0.77 , 1.22]**
Total events	136		130			
Heterogeneity Tau² = 0 00; Chi² = 3 84, df = 11 (P = 0 97); I² = 0%						
Test for overall effect Z = 0 27 (P = 0 79)						
Test for subgroup differences Chi² = 0 37, df = 2 (P = 0 83), I² = 0%						

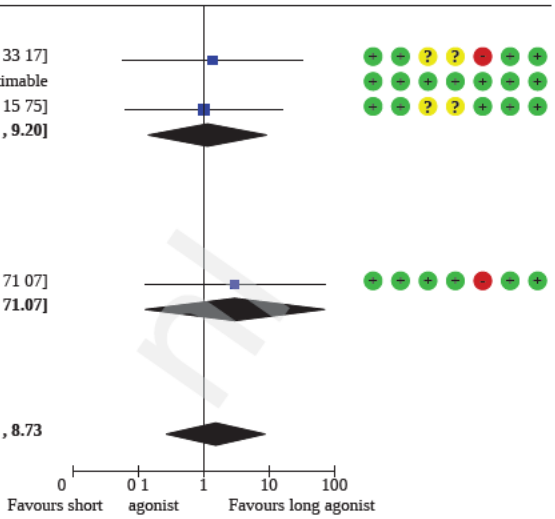


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 1.7. Comparison 1: Direct comparison: Short GnRH antagonist versus long GnRH agonist protocols, Outcome 7: Ectopic

Study or Subgroup	Short antagonist Events	Total	Long agonist Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Normal response						
Albano 2000	1	188	0	85	29 8%	1 37 [0 06 , 33 17]
Franco 2003	0	14	0	6		Not estimable
Huirne 2006	1	91	1	91	39 9%	1 00 [0 06 , 15 75]
Subtotal (95% CI)		**293**		**182**	**69.7%**	**1.14 [0.14 , 9.20]**
Total events:	2		1			
Heterogeneity: Tau² = 0 00; Chi² = 0 02, df = 1 (P = 0 88); I² = 0%						
Test for overall effect: Z = 0 12 (P = 0 90)						
1.7.2 Low response						
Cheung 2005	1	33	0	33	30 3%	3 00 [0 13 , 71 07]
Subtotal (95% CI)		**33**		**33**	**30.3%**	**3.00 [0.13 , 71.07]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0 68 (P = 0 50)						
Total (95% CI)		**326**		**215**	**100.0%**	**1.53 [0.27 , 8.73**
Total events:	3		1			
Heterogeneity: Tau² = 0 00; Chi² = 0 27, df = 2 (P = 0 87); I² = 0%						
Test for overall effect: Z = 0 48 (P = 0 63)						
Test for subgroup differences: Chi² = 0 25, df = 1 (P = 0 62), I² = 0%						

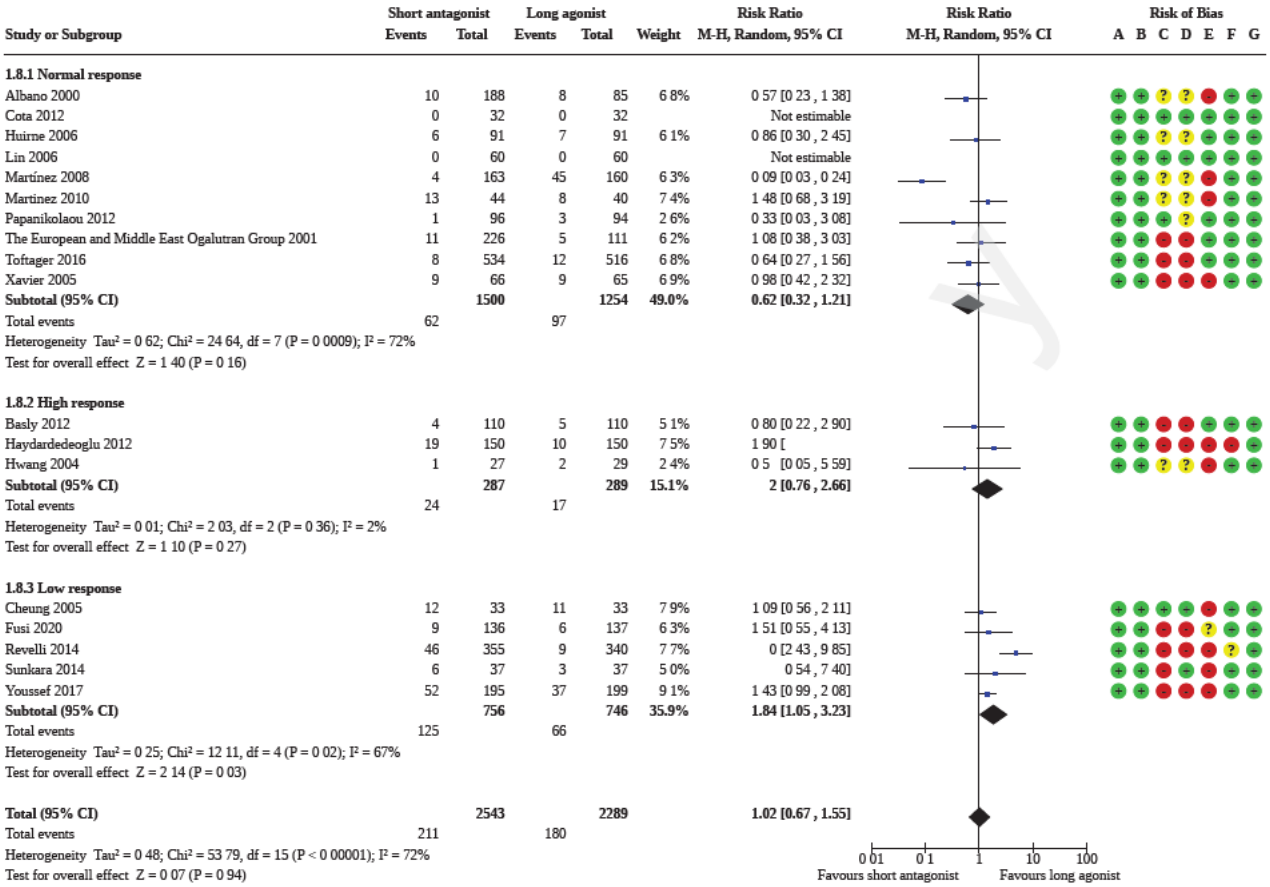


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 1.8. Comparison 1: Direct comparison: Short GnRH antagonist versus long GnRH agonist protocols, Outcome 8: Cancellation

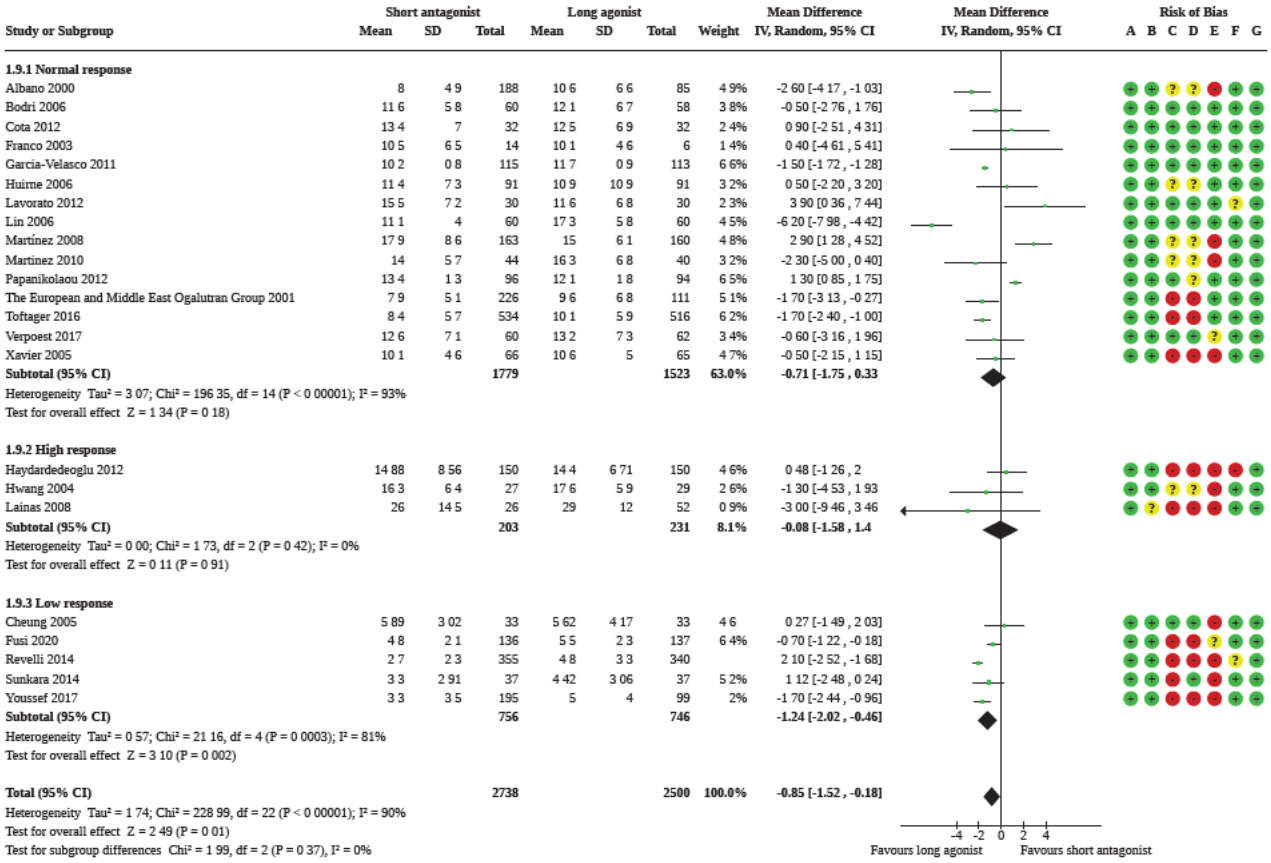


Study or Subgroup	Short antagonist Events	Short antagonist Total	Long agonist Events	Long agonist Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.8.1 Normal response							
Albano 2000	10	188	8	85	6 8%	0 57 [0 23 , 1 38]	
Cota 2012	0	32	0	32		Not estimable	
Huirne 2006	6	91	7	91	6 1%	0 86 [0 30 , 2 45]	
Lin 2006	0	60	0	60		Not estimable	
Martínez 2008	4	163	45	160	6 3%	0 09 [0 03 , 0 24]	
Martinez 2010	13	44	8	40	7 4%	1 48 [0 68 , 3 19]	
Papanikolaou 2012	1	96	3	94	2 6%	0 33 [0 03 , 3 08]	
The European and Middle East Ogalutran Group 2001	11	226	5	111	6 2%	1 08 [0 38 , 3 03]	
Toftager 2016	8	534	12	516	6 8%	0 64 [0 27 , 1 56]	
Xavier 2005	9	66	9	65	6 9%	0 98 [0 42 , 2 32]	
Subtotal (95% CI)		**1500**		**1254**	**49.0%**	**0.62 [0.32 , 1.21]**	
Total events	62		97				
Heterogeneity Tau² = 0 62; Chi² = 24 64, df = 7 (P = 0 0009); I² = 72%							
Test for overall effect Z = 1 40 (P = 0 16)							
1.8.2 High response							
Basly 2012	4	110	5	110	5 1%	0 80 [0 22 , 2 90]	
Haydardedeoglu 2012	19	150	10	150	7 5%	1 90 [	
Hwang 2004	1	27	2	29	2 4%	0 5 [0 05 , 5 59]	
Subtotal (95% CI)		**287**		**289**	**15.1%**	**2 [0.76 , 2.66]**	
Total events	24		17				
Heterogeneity Tau² = 0 01; Chi² = 2 03, df = 2 (P = 0 36); I² = 2%							
Test for overall effect Z = 1 10 (P = 0 27)							
1.8.3 Low response							
Cheung 2005	12	33	11	33	7 9%	1 09 [0 56 , 2 11]	
Fusi 2020	9	136	6	137	6 3%	1 51 [0 55 , 4 13]	
Revelli 2014	46	355	9	340	7 7%	0 [2 43 , 9 85]	
Sunkara 2014	6	37	3	37	5 0%	0 54 , 7 40]	
Youssef 2017	52	195	37	199	9 1%	1 43 [0 99 , 2 08]	
Subtotal (95% CI)		**756**		**746**	**35.9%**	**1.84 [1.05 , 3.23]**	
Total events	125		66				
Heterogeneity Tau² = 0 25; Chi² = 12 11, df = 4 (P = 0 02); I² = 67%							
Test for overall effect Z = 2 14 (P = 0 03)							
Total (95% CI)		**2543**		**2289**		**1.02 [0.67 , 1.55]**	
Total events	211		180				
Heterogeneity Tau² = 0 48; Chi² = 53 79, df = 15 (P < 0 00001); I² = 72%							
Test for overall effect Z = 0 07 (P = 0 94)							
Test for subgroup differences Chi² = 6 27, df = 2 (P = 0 04), I² = 68 1%							

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 1.9. Comparison 1: Direct comparison: Short GnRH antagonist versus long GnRH agonist protocols, Outcome 9: Oocyte number

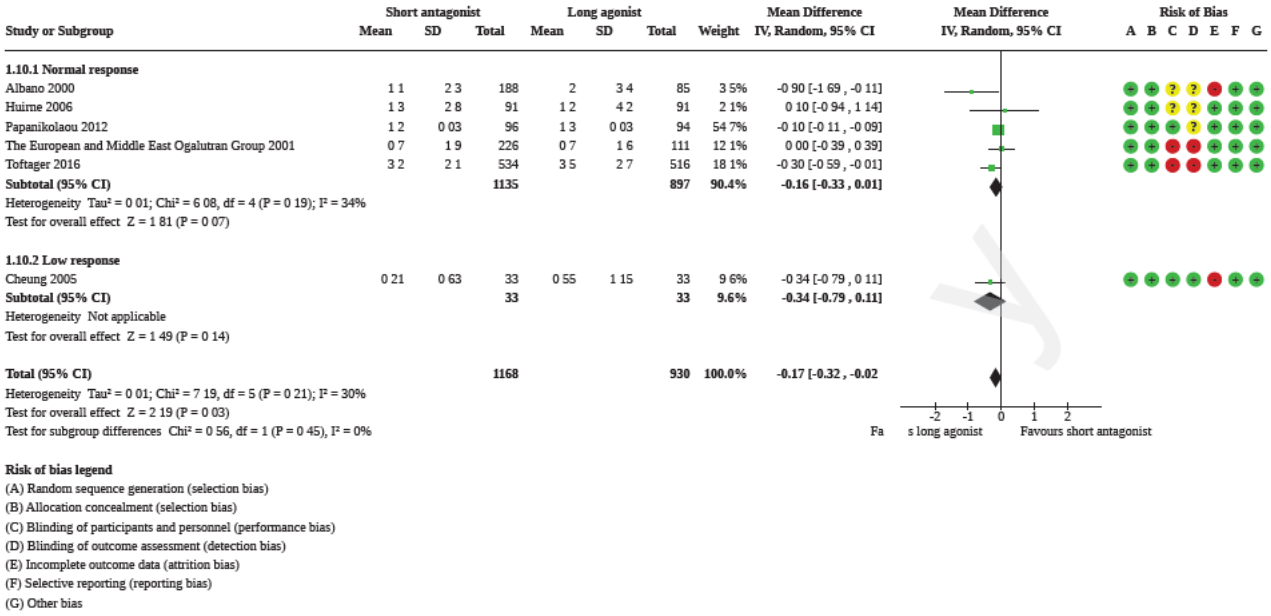


Study or Subgroup	Short antagonist Mean	SD	Total	Long agonist Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
1.9.1 Normal response									
Albano 2000	8	4 9	188	10 6	6 6	85	4 9%	-2 60 [-4 17 , -1 03]	+ + ? ? - + +
Bodri 2006	11 6	5 8	60	12 1	6 7	58	3 8%	-0 50 [-2 76 , 1 76]	+ + - - + + +
Cota 2012	13 4	7	32	12 5	6 9	32	2 4%	0 90 [-2 51 , 4 31]	+ + - - + + +
Franco 2003	10 5	6 5	14	10 1	4 6	6	1 4%	0 40 [-4 61 , 5 41]	+ + - - + + +
Garcia-Velasco 2011	10 2	0 8	115	11 7	0 9	113	6 6%	-1 50 [-1 72 , -1 28]	+ + - - + + +
Huirne 2006	11 4	7 3	91	10 9	10 9	91	3 2%	0 50 [-2 20 , 3 20]	+ + ? ? + + +
Lavorato 2012	15 5	7 2	30	11 6	6 8	30	2 3%	3 90 [0 36 , 7 44]	+ + - - + ? +
Lin 2006	11 1	4	60	17 3	5 8	60	4 5%	-6 20 [-7 98 , -4 42]	+ + - - + + +
Martínez 2008	17 9	8 6	163	15	6 1	160	4 8%	2 90 [1 28 , 4 52]	+ + ? ? - + +
Martinez 2010	14	5 7	44	16 3	6 8	40	3 2%	-2 30 [-5 00 , 0 40]	+ + ? ? - + +
Papanikolaou 2012	13 4	1 3	96	12 1	1 8	94	6 5%	1 30 [0 85 , 1 75]	+ + - ? + + +
The European and Middle East Ogalutran Group 2001	7 9	5 1	226	9 6	6 8	111	5 1%	-1 70 [-3 13 , -0 27]	+ + - - + + +
Toftager 2016	8 4	5 7	534	10 1	5 9	516	6 2%	-1 70 [-2 40 , -1 00]	+ + - - + + +
Verpoest 2017	12 6	7 1	60	13 2	7 3	62	3 4%	-0 60 [-3 16 , 1 96]	+ + - - ? + +
Xavier 2005	10 1	4 6	66	10 6	5	65	4 7%	-0 50 [-2 15 , 1 15]	+ + - - - + +
Subtotal (95% CI)			**1779**			**1523**	**63.0%**	**-0.71 [-1.75 , 0.33**	
Heterogeneity Tau² = 3 07; Chi² = 196 35, df = 14 (P < 0 00001); I² = 93%									
Test for overall effect Z = 1 34 (P = 0 18)									
1.9.2 High response									
Haydardedeoglu 2012	14 88	8 56	150	14 4	6 71	150	4 6%	0 48 [-1 26 , 2	+ + - - - - +
Hwang 2004	16 3	6 4	27	17 6	5 9	29	2 6%	-1 30 [-4 53 , 1 93	+ + ? ? - + +
Lainas 2008	26	14 5	26	29	12	52	0 9%	-3 00 [-9 46 , 3 46	+ ? - - - + +
Subtotal (95% CI)			**203**			**231**	**8.1%**	**-0.08 [-1.58 , 1.4**	
Heterogeneity Tau² = 0 00; Chi² = 1 73, df = 2 (P = 0 42); I² = 0%									
Test for overall effect Z = 0 11 (P = 0 91)									
1.9.3 Low response									
Cheung 2005	5 89	3 02	33	5 62	4 17	33	4 6	0 27 [-1 49 , 2 03]	+ + + - - + +
Fusi 2020	4 8	2 1	136	5 5	2 3	137	6 4%	-0 70 [-1 22 , -0 18]	+ + - - ? + +
Revelli 2014	2 7	2 3	355	4 8	3 3	340		2 10 [-2 52 , -1 68]	+ + - - - ? +
Sunkara 2014	3 3	2 91	37	4 42	3 06	37	5 2%	1 12 [-2 48 , 0 24]	+ + - + - + +
Youssef 2017	3 3	3 5	195	5	4	99	2%	-1 70 [-2 44 , -0 96]	+ + - - - + +
Subtotal (95% CI)			**756**			**746**		**-1.24 [-2.02 , -0.46]**	
Heterogeneity Tau² = 0 57; Chi² = 21 16, df = 4 (P = 0 0003); I² = 81%									
Test for overall effect Z = 3 10 (P = 0 002)									
Total (95% CI)			**2738**			**2500**	**100.0%**	**-0.85 [-1.52 , -0.18]**	
Heterogeneity Tau² = 1 74; Chi² = 228 99, df = 22 (P < 0 00001); I² = 90%									
Test for overall effect Z = 2 49 (P = 0 01)									
Test for subgroup differences Chi² = 1 99, df = 2 (P = 0 37), I² = 0%									

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 1.10. Comparison 1: Direct comparison: Short GnRH antagonist versus long GnRH agonist protocols, Outcome 10: Frozen embryo number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

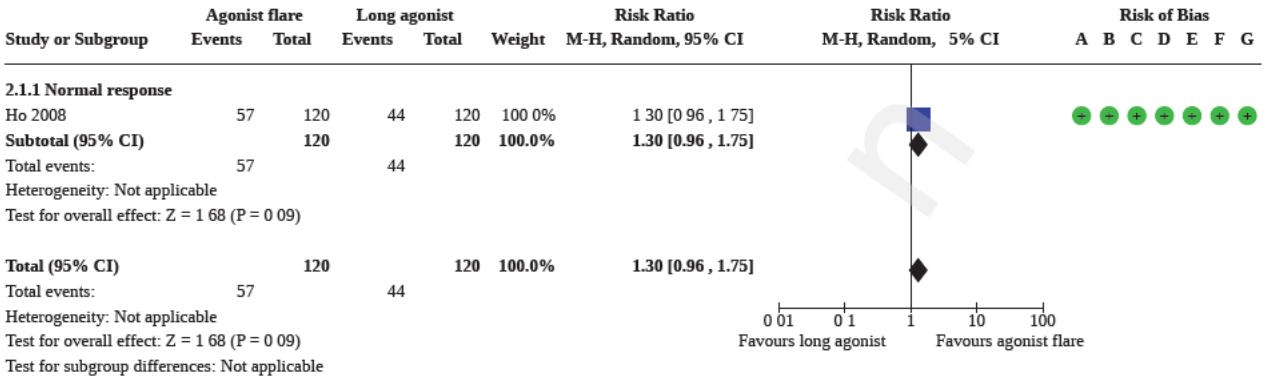
Comparison 2. Direct comparison: GnRH agonist flare versus l ng GnRH agonist protocols

Outcome or subgroup title	No. of studies	No. of partici-pants	tat stical method	Effect size
2.1 Live birth	1	240	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.96, 1.75]
2.1.1 Normal response	1	240	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.96, 1.75]
2.2 Clinical pregnancy	2	33	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.35, 2.08]
2.2.1 Normal response	2	331	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.35, 2.08]
2.3 Ongoing pregnancy	2	314	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.92, 1.62]
2.3.1 Normal response	1	240	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.92, 1.63]
2.3.2 Low response	1	74	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.22, 4.64]
2.4 Ectopic	1	240	Risk Ratio (M-H, Random, 95% CI)	2.50 [0.49, 12.64]
2.4.1 Normal response	1	240	Risk Ratio (M-H, Random, 95% CI)	2.50 [0.49, 12.64]
2.5 Cancellation	3	625	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.58, 3.62]
2.5.1 Normal response	2	551	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.46, 5.07]
2.5.2 Low response	1	74	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.32, 5.55]
2.6 Oocyte number	2	314	Mean Difference (IV, Random, 95% CI)	-2.40 [-3.95, -0.86]
2.6.1 Normal response	1	240	Mean Difference (IV, Random, 95% CI)	-3.30 [-4.87, -1.73]

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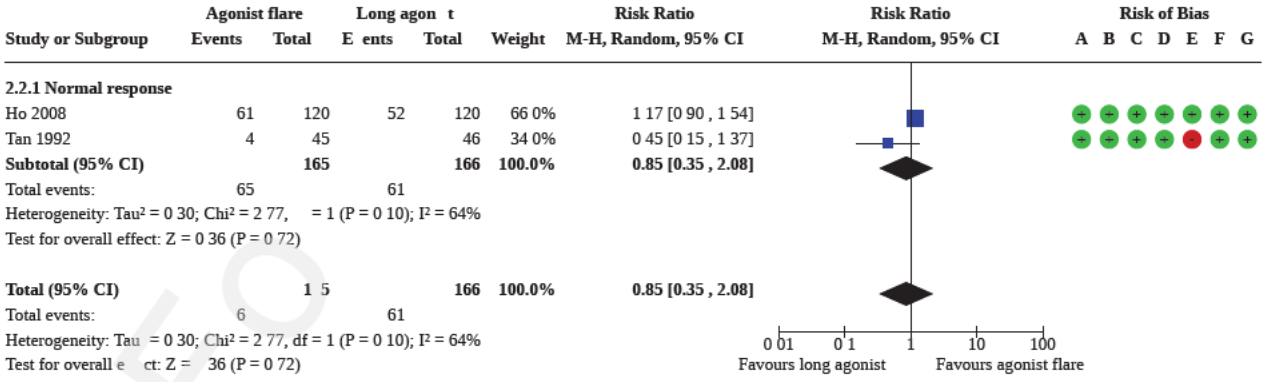
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6.2 Low response	1	74	Mean Difference (IV, Random, 95% CI)	-1.71 [-2.82, -0.60]

Analysis 2.1. Comparison 2: Direct comparison: GnRH agonist flare versus long GnRH agonist protocols, Outcome 1: Live birth



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparis n 2: Direct comparison: GnRH agonist flare versus long GnRH agonist rotocols, Outcome 2: Clinical pregnancy

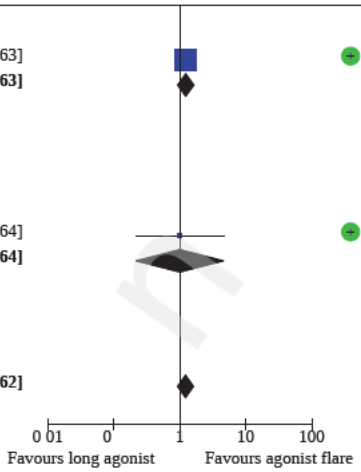


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 2.3. Comparison 2: Direct comparison: GnRH agonist flare versus long GnRH agonist protocols, Outcome 3: Ongoing pregnancy

Study or Subgroup	Agonist flare Events	Total	Long agonist Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Normal response						
Ho 2008	59	120	48	120	96 7%	1 23 [0 92 , 1 63]
Subtotal (95% CI)		**120**		**120**	**96.7%**	**1.23 [0.92 , 1.63]**
Total events:	59		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1 42 (P = 0 16)						
2.3.2 Low response						
Sunkara 2014	3	37	3	37	3 3%	1 00 [0 22 , 4 64]
Subtotal (95% CI)		**37**		**37**	**3.3%**	**1.00 [0.22 , 4.64]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0 00 (P = 1 00)						
Total (95% CI)		**157**		**157**	**100.0%**	**1.22 [0.92 , 1.62]**
Total events:	62		51			
Heterogeneity: Tau² = 0 00; Chi² = 0 07, df = 1 (P = 0 79); I² = 0%						
Test for overall effect: Z = 1 40 (P = 0 16)						
Test for subgroup differences: Chi² = 0 07, df = 1 (P = 0 80), I² = 0%						

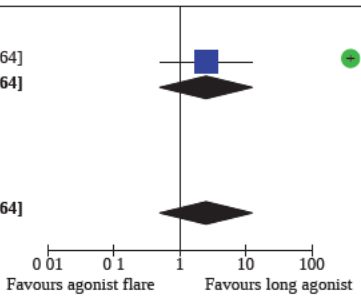




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.4. Comparison 2: Direct comparison: GnRH agonist flare versus long GnRH agonist protocols, Outcome 4: Ectopic

Study or Subgroup	Agonist flare Events	Total	Long agonist Ev	To l	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Normal response						
Ho 2008	5	120	2	120	100 0%	2 50 [0 49 , 12 64]
Subtotal (95% CI)		**120**		**120**	**100.0%**	**2.50 [0.49 , 12.64]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1 11 (P = 0 27						
Total (95% CI)		**120**		**120**	**100.0%**	**2.50 [0.49 , 12.64]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1 11 (P 0 27)						
Test for subgroup differences: Not applicable						

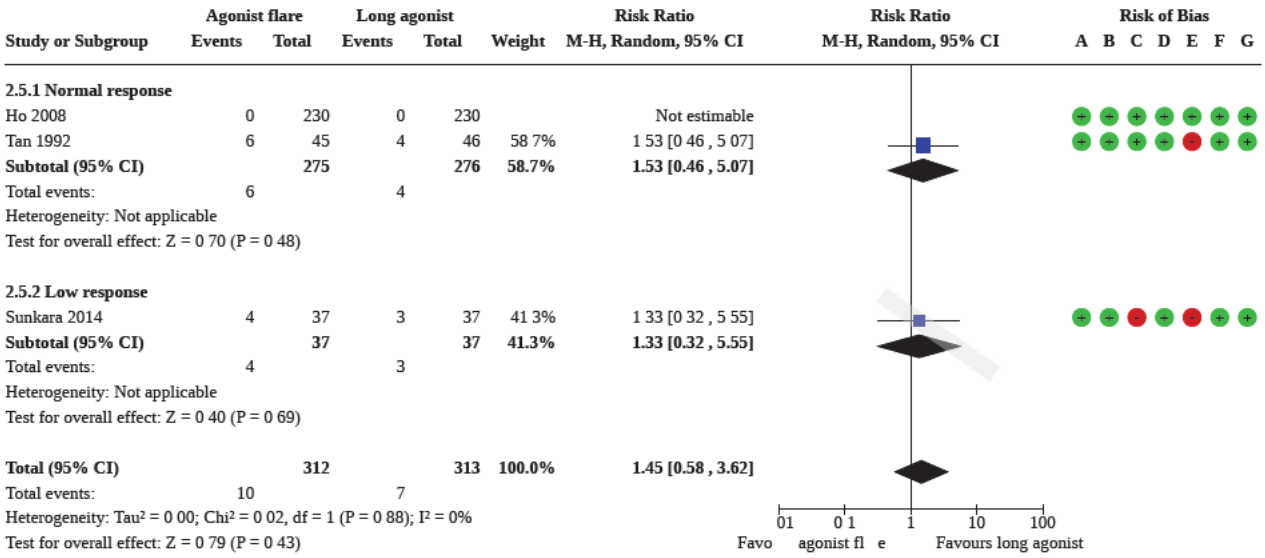




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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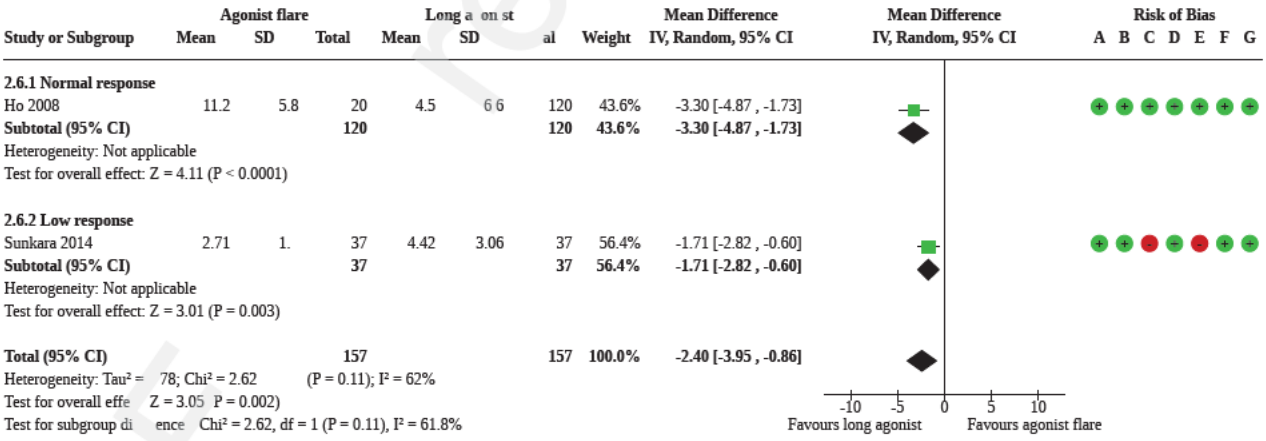
Analysis 2.5. Comparison 2: Direct comparison: GnRH agonist flare versus long GnRH agonist protocols, Outcome 5: Cancellation



Study or Subgroup	Agonist flare Events	Total	Long agonist Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Normal response						
Ho 2008	0	230	0	230		Not estimable
Tan 1992	6	45	4	46	58 7%	1 53 [0 46 , 5 07]
Subtotal (95% CI)		**275**		**276**	**58.7%**	**1.53 [0.46 , 5.07]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0 70 (P = 0 48)						
2.5.2 Low response						
Sunkara 2014	4	37	3	37	41 3%	1 33 [0 32 , 5 55]
Subtotal (95% CI)		**37**		**37**	**41.3%**	**1.33 [0.32 , 5.55]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0 40 (P = 0 69)						
Total (95% CI)		**312**		**313**	**100.0%**	**1.45 [0.58 , 3.62]**
Total events:	10		7			
Heterogeneity: Tau² = 0 00; Chi² = 0 02, df = 1 (P = 0 88); I² = 0%						
Test for overall effect: Z = 0 79 (P = 0 43)						
Test for subgroup differences: Chi² = 0 02, df = 1 (P = 0 88), I² = 0%						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.6. Comparison 2 D rect comparison: GnRH agonist flare versus long GnRH ago ist protocols, Outcome 6: Oocyte number



Study or Subgroup	Agonist flare Mean	SD	Total	Long a on st Mean	SD	al	Weight	Mean Difference IV, Random, 95% CI
2.6.1 Normal response								
Ho 2008	11.2	5.8	20	4.5	6 6	120	43.6%	-3.30 [-4.87 , -1.73]
Subtotal (95% CI)			**120**			**120**	**43.6%**	**-3.30 [-4.87 , -1.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.11 (P < 0.0001)								
2.6.2 Low response								
Sunkara 2014	2.71	1.	37	4.42	3.06	37	56.4%	-1.71 [-2.82 , -0.60]
Subtotal (95% CI)			**37**			**37**	**56.4%**	**-1.71 [-2.82 , -0.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.01 (P = 0.003)								
Total (95% CI)			**157**			**157**	**100.0%**	**-2.40 [-3.95 , -0.86]**
Heterogeneity: Tau² = 78; Chi² = 2.62 (P = 0.11); I² = 62%								
Test for overall effe Z = 3.05 P = 0.002)								
Test for subgroup di ence Chi² = 2.62, df = 1 (P = 0.11), I² = 61.8%								

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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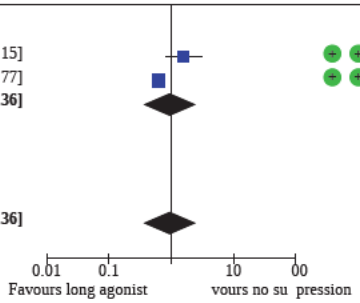
Comparison 3. Direct comparison: No pituitary suppression versus long GnRH agonist protocols

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Live birth	2	714	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.38, 2.36]
3.1.1 Normal response	2	714	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.38, 2.36]
3.2 Clinical pregnancy	3	758	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.54, 1.09]
3.2.1 Normal response	2	720	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.49, 1.21]
3.2.2 Low response	1	38	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.29, 3.23]
3.3 Multiple pregnancy	2	714	Risk Ratio (M-H, Random, 95 CI)	0.27 [0.07, 1.04]
3.3.1 Normal response	2	714	Risk Ratio (M H, Ra dom, 95% CI)	0.27 [0.07, 1.04]
3.4 Miscarriage	1	150	Risk Ratio M-H, Random, 95% CI)	1.33 [0.39, 4.51]
3.4.1 Normal response	1	150	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.39, 4.51]
3.5 Cancellation	3	752	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.21, 3.06]
3.5.1 Normal response	2	714	Risk Ra io (M-H, Random, 95% CI)	0.67 [0.13, 3.35]
3.5.2 Low response	1	38	R sk Ratio (M-H, Random, 95% CI)	1.92 [0.13, 28.32]
3.6 Oocyte number	3	752	Mean Difference (IV, Random, 95% CI)	-3.99 [-9.77, 1.80]
3.6.1 Normal response	2	714	Mean Difference (IV, Random, 95% CI)	-5.80 [-11.24, -0.36]
3.6.2 Low response	1	38	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.01, 0.01]
3.7 Blastocyst number	1	564	Mean Difference (IV, Random, 95% CI)	-3.30 [-3.85, -2.75]
3.7.1 Normal response	1	564	Mean Difference (IV, Random, 95% CI)	-3.30 [-3.85, -2.75]

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Analysis 3.1. Comparison 3: Direct comparison: No pituitary suppression versus long GnRH agonist protocols, Outcome 1: Live birth

Study or Subgroup	No pituitary suppression Events	Total	Long agonist Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Normal response						
Harrison 1994	12	50	15	100	43.9%	1.60 [0.81 , 3.15]
Zhang 2016	90	285	141	279	56.1%	0.62 [0.51 , 0.77]
Subtotal (95% CI)		**335**		**379**	**100.0%**	**0.94 [0.38 , 2.36]**
Total events:	102		156			
Heterogeneity: Tau² = 0.38; Chi² = 6.77, df = 1 (P = 0.009); I² = 85%						
Test for overall effect: Z = 0.12 (P = 0.90)						
Total (95% CI)		**335**		**379**	**100.0%**	**0.94 [0.38 , 2.36]**
Total events:	102		156			
Heterogeneity: Tau² = 0.38; Chi² = 6.77, df = 1 (P = 0.009); I² = 85%						
Test for overall effect: Z = 0.12 (P = 0.90)						
Test for subgroup differences: Not applicable						

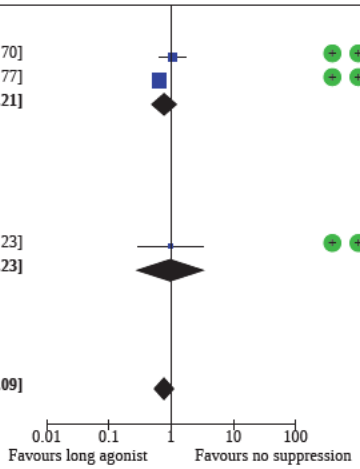


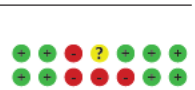


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.2. Comparison 3: Direct compari on: No pituitary suppression versus long GnRH agonist protocols Outcome 2: Clinical pregnancy

Study or Subgroup	No pituitary suppression Events	Total	Long agonist Events	Total	Weight	M	Risk atio Rand m, 95% CI
3.2.1 Normal response							
Harrison 1994	16	50	31	100	30. %		1.03 [0.63 , 1.70]
Zhang 2016	106	285	165	28	62 3%		0.64 [0.54 , 0.77]
Subtotal (95% CI)		**335**		**385**	**92.3%**		**0.77 [0.49 , 1.21]**
Total events:	122		196				
Heterogeneity: Tau² = 0.08; Chi² = 3.09, df = 1 (P = 0.08); I² = 68%							
Test for overall effect: Z = 1.15 (P = 0.25)							
3.2.2 Low response							
Goswami 2004	3	13	6	25	7.7%		0.96 [0.29 , 3.23]
Subtotal (95% CI)		**13**		**25**	**7.7%**		**0.96 [0.29 , 3.23]**
Total events:	3		6				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.06 (P = 0.95)							
Total (95% CI)		**348**		**410**	**100.0%**		**0.76 [0.54 , 1.09]**
Total events:	125		202				
Heterogeneity: Tau² = 0.04; Chi² = 3.40, df = (P = 0.18); I² = 41%							
Test for overall effect: Z = 1.49 (P =							
Test for subgroup differences: Ch = 0.12, df 1 (P = 0.73), I² = 0%							



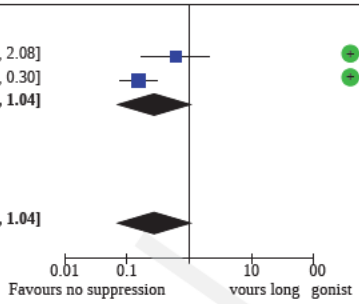


Risk of bias legend
(A) Random sequen e genera n (selection bias)
(B) Allocation con alment election bias)
(C) Blinding of particip and personnel (performance bias)
(D) Blinding of outcome ass ment (detection bias)
(E) Incomplete outcome data (att ition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 3.3. Comparison 3: Direct comparison: No pituitary suppression versus long GnRH agonist protocols, Outcome 3: Multiple pregnancy

Study or Subgroup	No pituitary suppression Events	Total	Long agonist Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Normal response						
Harrison 1994	3	50	10	100	42.6%	0.60 [0.17 , 2.08]
Zhang 2016	9	285	58	279	57.4%	0.15 [0.08 , 0.30]
Subtotal (95% CI)		**335**		**379**	**100.0%**	**0.27 [0.07 , 1.04]**
Total events:	12		68			
Heterogeneity: Tau² = 0.69; Chi² = 3.63, df = 1 (P = 0.06); I² = 72%						
Test for overall effect: Z = 1.90 (P = 0.06)						
Total (95% CI)		**335**		**379**	**100.0%**	**0.27 [0.07 , 1.04]**
Total events:	12		68			
Heterogeneity: Tau² = 0.69; Chi² = 3.63, df = 1 (P = 0.06); I² = 72%						
Test for overall effect: Z = 1.90 (P = 0.06)						
Test for subgroup differences: Not applicable						

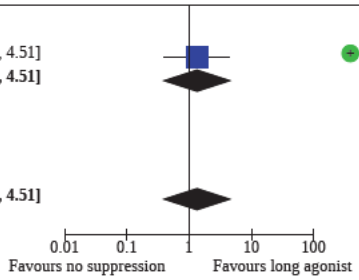




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.4. Comparison 3: Direct comparison: No pituitary suppression versus long GnRH agonist protocols, Outcome 4: Miscarriage

Study or Subgroup	No pituitary suppression Events	Total	Long agonist Events	Total	Weight	Risk atio M Rand m, 95% CI
3.4.1 Normal response						
Harrison 1994	4	50	6	100	100. %	1.33 [0.39 , 4.51]
Subtotal (95% CI)		**50**		**10**	**100 0%**	**1.33 [0.39 , 4.51]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
Total (95% CI)		**50**			**100.0%**	**1.33 [0.39 , 4.51]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
Test for subgroup differences: Not applicable						



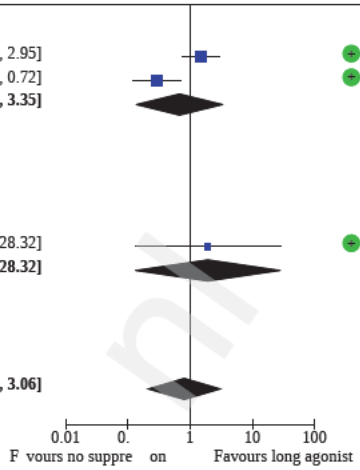


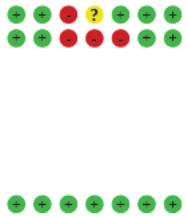
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personne (erformance bias)
(D) Blinding of outcome assessment (detectio bias)
(E) Incomplete outcome data (attriti
(F) Selective reporting (reporting as)
(G) Other bias

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Analysis 3.5. Comparison 3: Direct comparison: No pituitary suppression versus long GnRH agonist protocols, Outcome 5: Cancellation

Study or Subgroup	No pituitary suppression Events	Total	Long agonist Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Normal response						
Harrison 1994	11	50	15	100	43.3%	1.47 [0.73 , 2.95]
Zhang 2016	6	285	20	279	40.2%	0.29 [0.12 , 0.72]
Subtotal (95% CI)		**335**		**379**	**83.5%**	**0.67 [0.13 , 3.35]**
Total events:	17		35			
Heterogeneity: Tau² = 1.18; Chi² = 7.98, df = 1 (P = 0.005); I² = 87%						
Test for overall effect: Z = 0.48 (P = 0.63)						
3.5.2 Low response						
Goswami 2004	1	13	1	25	16.5%	1.92 [0.13 , 28.32]
Subtotal (95% CI)		**13**		**25**	**16.5%**	**1.92 [0.13 , 28.32]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**348**		**404**	**100.0%**	**0.80 [0.21 , 3.06]**
Total events:	18		36			
Heterogeneity: Tau² = 0.95; Chi² = 8.37, df = 2 (P = 0.02); I² = 76%						
Test for overall effect: Z = 0.32 (P = 0.75)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						

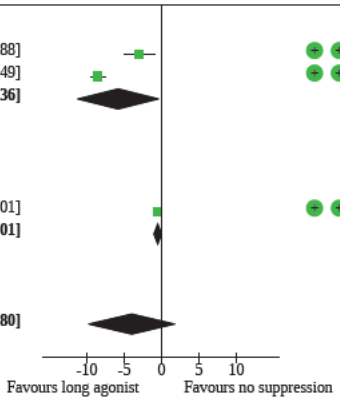


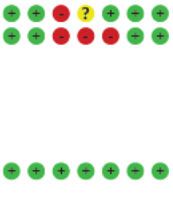


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.6. Comparison 3: D rect c mparison: No pituitary suppression versus long GnRH agonist protocols, Outcome 6: Oocyte number

Study or Subgroup	No pituitary suppression Mean	SD	Total	Long gonist Mean	D	Tot	Weight	Mean Difference IV, Random, 95% CI
3.6.1 Normal response								
Harrison 1994	8.82	4.35	50	11	8.57	100	32.5%	-2.95 [-5.02 , -0.88]
Zhang 2016	4.3	3.2	2	12.8	8	279	33.6%	-8.50 [-9.51 , -7.49]
Subtotal (95% CI)			**335**			**379**	**66.1%**	**-5.80 [-11.24 , -0.36]**
Heterogeneity: Tau² = 14.71; Chi² = 22.35, df = 1 < 0.00001 I² = 96%								
Test for overall effect: Z = 2.09 (P = 0.04)								
3.6.2 Low response								
Goswami 2004	1.6	0.8	13	2.1	0.7	25	33.9%	-0.50 [-1.01 , 0.01]
Subtotal (95% CI)			**13**			**25**	**33.9%**	**-0.50 [-1.01 , 0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.91 (P = 0.06)								
Total (95% CI)			**348**			**404**	**100.0%**	**-3.99 [-9.77 , 1.80]**
Heterogeneity: Tau² = 25 2; Chi² = 92.08, df = (P < 0.00001); I² = 99%								
Test for overall effect: = 1.35 (P = 0)								
Test for subgroup dif rences: C ² = 3.62, df = 1 (P = 0.06), I² = 72.4%								

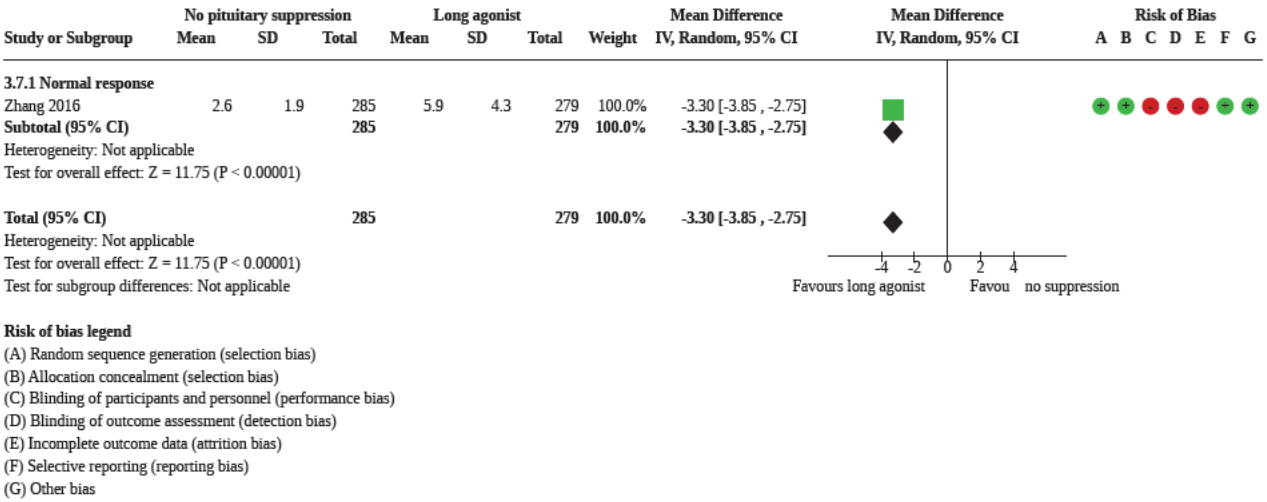




Risk of bias legend
(A) Random sequence genera n (selection bias)
(B) Allocation concealment (selec on bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 3.7. Comparison 3: Direct comparison: No pituitary suppression versus long GnRH agonist protocols, Outcome 7: Blastocyst number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

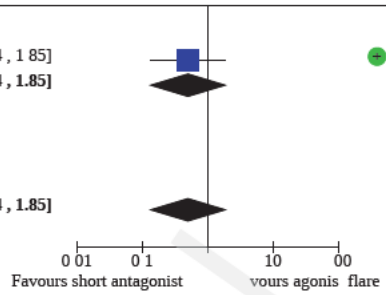
Comparison 4. Direct comparison: GnRH agonist flare versus short GnRH antagonist protocols

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Ongoing pregnancy	1	74	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.14, 1.85]
4.1.1 Low response	1	74	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.14, 1.85]
4.2 Cancellation	1	74	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.46, 4.88]
4.2.1 Low response	1	74	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.46, 4.88]
4.3 Oocyte number	1	7	Mean Difference (IV, Random, 95% CI)	-0.59 [-1.66, 0.48]
4.3.1 Low response	1	74	Mean Difference (IV, Random, 95% CI)	-0.59 [-1.66, 0.48]

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Analysis 4.1. Comparison 4: Direct comparison: GnRH agonist flare versus short GnRH antagonist protocols, Outcome 1: Ongoing pregnancy

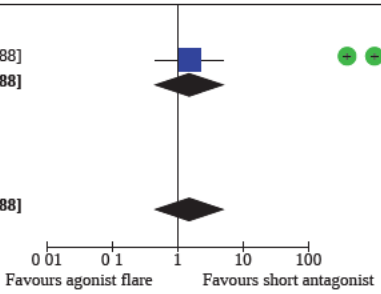
Study or Subgroup	Agonist flare Events	Total	Short antagonist Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Low response						
Sunkara 2014	3	37	6	37	100 0%	0 50 [0 14 , 1 85]
Subtotal (95% CI)		**37**		**37**	**100.0%**	**0.50 [0.14 , 1.85]**
Total events:	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1 04 (P = 0 30)						
Total (95% CI)		**37**		**37**	**100.0%**	**0.50 [0.14 , 1.85]**
Total events:	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1 04 (P = 0 30)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.2. Comparison 4: Direct mp rison: GnRH agonist flare versus short GnRH antagonist pr ocols, Outcome 2: Cancellation

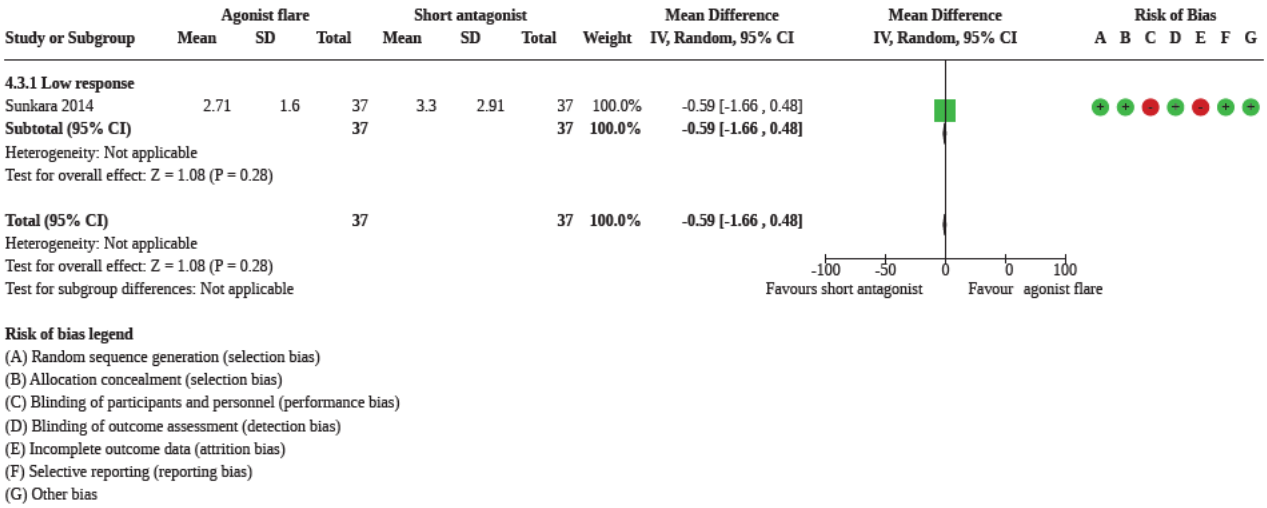
Study or Subgroup	Short antagonist Events	Total	Agonist flare Events	Total	Weight	Ri k Rati M H, Ra d , 95% CI
4.2.1 Low response						
Sunkara 2014	6	37	4	37	100 0%	1 50 [0 46 , 4 88]
Subtotal (95% CI)		**37**		**37**	**100.0%**	**1.50 [0.46 , 4.88]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0 67 (P = 0 50)						
Total (95% CI)		**37**		**37**	**100.0%**	**1.50 [0.46 , 4.88]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0 67 (P = 0 50)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (select n bias)
(B) Allocation concealment (selection b)
(C) Blinding of participants and personnel (p formance bias)
(D) Blinding of outcome assessm nt (de ion bias)
(E) Incomplete outcome data (a rition bias)
(F) Selective reporting (reporting ias)
(G) Other bias

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Analysis 4.3. Comparison 4: Direct comparison: GnRH agonist flare versus short GnRH antagonist protocols, Outcome 3: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

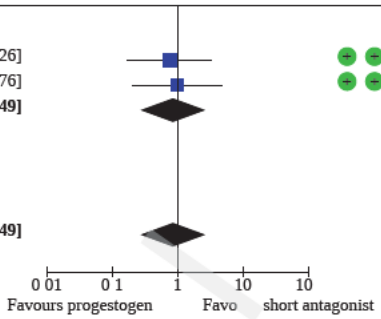
Comparison 5. Direct comparison: Progestogens versus short GnRH antagonist protocols

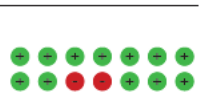
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Cancellation	2	512	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.29, 2.49]
5.1.1 Normal response	2	512	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.29, 2.49]
5.2 Oocyte number	1	318	Mean Difference (IV, Random, 95% CI)	0.20 [-2.11, 2.51]
5.2.1 Normal response	1	31	Mean Difference (IV, Random, 95% CI)	0.20 [-2.11, 2.51]
5.3 Blastocyst number	1	31	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.74, 0.34]
5.3.1 Normal response	1	18	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.74, 0.34]

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Analysis 5.1. Comparison 5: Direct comparison: Progestogens versus short GnRH antagonist protocols, Outcome 1: Cancellation

Study or Subgroup	Progestogen Events	Progestogen Total	Short antagonist Events	Short antagonist Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Normal response						
Begueria 2019	3	97	4	97	53 8%	0 75 [0 17 , 3 26]
Giles 2021	3	161	3	157	46 2%	0 98 [0 20 , 4 76]
Subtotal (95% CI)		**258**		**254**	**100.0%**	**0.85 [0.29 , 2.49]**
Total events:	6		7			
Heterogeneity: Tau² = 0 00; Chi² = 0 06, df = 1 (P = 0 81); I² = 0%						
Test for overall effect: Z = 0 30 (P = 0 76)						
Total (95% CI)		**258**		**254**	**100.0%**	**0.85 [0.29 , 2.49]**
Total events:	6		7			
Heterogeneity: Tau² = 0 00; Chi² = 0 06, df = 1 (P = 0 81); I² = 0%						
Test for overall effect: Z = 0 30 (P = 0 76)						
Test for subgroup differences: Not applicable						

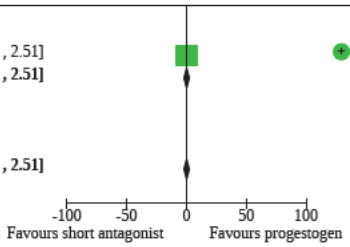




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.2. Comparison 5: Direct comparison: Progestogens versus short GnRH antagonist proto ol , Outcome 2: Oocyte number

Study or Subgroup	Progestogen Mean	Progestogen SD	Progestogen Total	Short antagonist Mean	Short antagonist SD	Short antagonist Tota	We ht	M an Difference IV, Random, 95% CI
5.2.1 Normal response								
Giles 2021	21.4	11.7	161	21.2	9.2	57	00.0%	0.20 [-2.11 , 2.51]
Subtotal (95% CI)			**161**			**157**	**100.0%**	**0.20 [-2.11 , 2.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.17 (P = 0.87)								
Total (95% CI)			**161**			**157**	**100.0%**	**0.20 [-2.11 , 2.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.17 (P = 0.87)								
Test for subgroup differences: Not applicable								

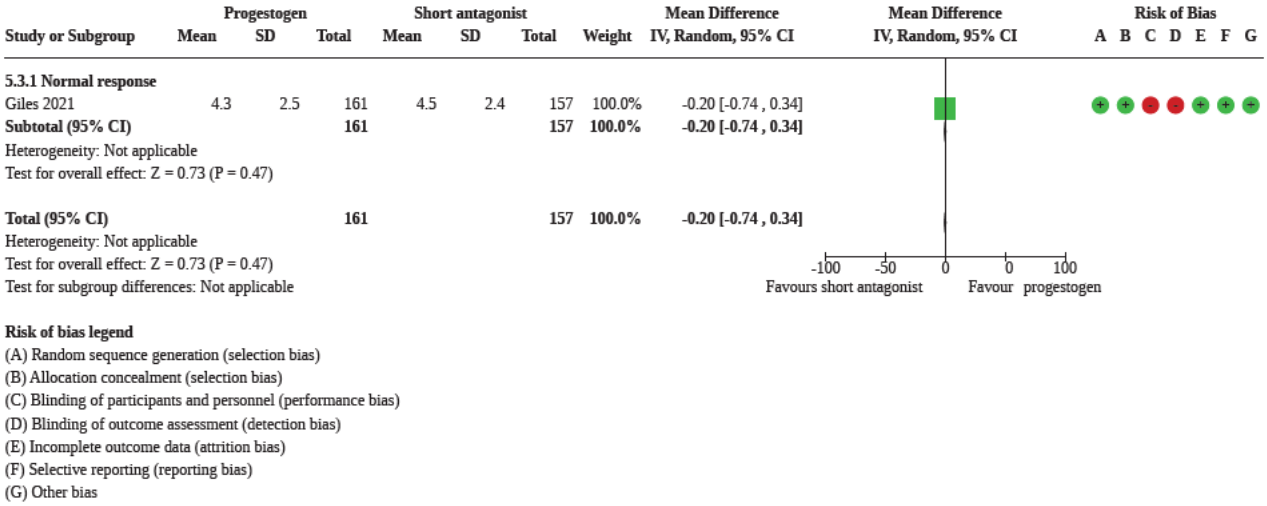




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (pe ormance bias)
(D) Blinding of outcome assessment (detecti n bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 5.3. Comparison 5: Direct comparison: Progestogens versus short GnRH antagonist protocols, Outcome 3: Blastocyst number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 6. Direct comparison: Long GnRH agonist plus uFSH versus long GnRH agonist plus rFSH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Live birth	6	1353	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.17]
6.1.1 Normal response	5	1193	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.19]
6.1.2 High response	1	160	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.63, 1.99]
6.2 OHSS	4	537	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.48, 1.94]
6.2.1 Normal response	3	377	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.32, 2.12]
6.2.2 High response	1	160	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.41, 3.32]
6.3 Clinical pregnancy	10	1830	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.15]
6.3.1 Normal response	8	1586	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.87, 1.16]
6.3.2 High response	2	244	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.79, 1.35]
6.4 Ongoing pregnancy	3	343	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.67, 1.39]
6.4.1 Normal response	1	99	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.23, 1.26]
6.4.2 High response	2	244	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.78, 1.48]
6.5 Multiple pregnancy	5	1162	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.78, 1.59]
6.5.1 Normal response	3	918	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.73, 1.87]
6.5.2 High response	2	244	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.51, 1.86]

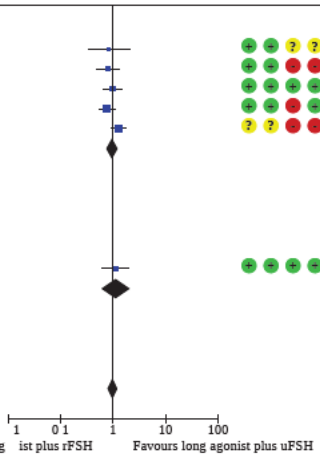
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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.6 Miscarriage	5	876	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.55, 1.59]
6.6.1 Normal response	4	716	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.51, 2.09]
6.6.2 High response	1	160	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.30, 1.99]
6.7 Ectopic	1	496	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.18, 21.74]
6.7.1 Normal response	1	496	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.18, 21.74]
6.8 Cancellation	5	1088	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.60, 1.31]
6.8.1 Normal response	4	928	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.59, 1.29]
6.8.2 High response	1	160	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.12, 72.56]
6.9 Oocyte number	8	1562	Mean Difference (IV, Random, 95% CI)	0.10 [-0.60, 0.80]
6.9.1 Normal response	6	1318	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.82, 0.46]
6.9.2 High response	2	244	Mean Difference (IV, Random, 95% CI)	1.67 [-0.13, 3.47]
6.10 Cleavage embryo number	2	278	Mean Difference (IV, Random, 95% CI)	0.52 [-0.56, 1.60]
6.10.1 Normal response	2	278	Mean Difference (IV, Random, 95% CI)	0.52 [-0.56, 1.60]
6.11 Frozen embryo number	4	551	Mean Difference (IV, Random, 95% CI)	0.19 [-0.86, 1.23]
6.11.1 Normal response	2	30	Mean Difference (IV, Random, 95% CI)	-0.35 [-1.92, 1.21]
6.11.2 High response	2	244	Mean Difference (IV, Random, 95% CI)	0.94 [-1.11, 3.00]

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Analysis 6.1. Comparison 6: Direct comparison: Long GnRH agonist plus uFSH versus long GnRH agonist plus rFSH, Outcome 1: Live birth

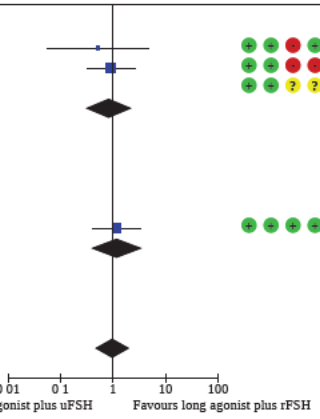
Study or Subgroup	Long agonist plus uFSH Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Normal response						
Recombinant Human FSH Study Group 1995	8	63	9	60	4 4%	0 85 [0 35 , 2 05]
Lenton 2000	20	75	27	80	14 0%	0 79 [0 49 , 1 28]
Baker 2009	29	76	29	76	19 5%	1 00 [0 67 , 1 50]
Schats 2000	43	249	56	247	24 4%	0 76 [0 53 , 1 09]
Selman 2002	52	133	41	134	27 6%	1 28 [0 92 , 1 78]
Subtotal (95% CI)		**596**		**597**	**89.9%**	**0.95 [0.76 , 1.19]**
Total events	152		162			
Heterogeneity Tau² = 0 02; Chi² = 5 25, df = 4 (P = 0 26); I² = 24%						
Test for overall effect Z = 0 44 (P = 0 66)						
6.1.2 High response						
Sohrabvand 2012	19	80	17	80	10 1%	1 12 [0 63 , 1 99]
Subtotal (95% CI)		**80**		**80**	**10.1%**	**1.12 [0.63 , 1.99]**
Total events	19		17			
Heterogeneity Not applicable						
Test for overall effect Z = 0 38 (P = 0 71)						
Total (95% CI)		**676**		**677**	**100.0%**	**0.97 [0 81 1.17]**
Total events	171		179			
Heterogeneity Tau² = 0 00; Chi² = 5 48, df = 5 (P = 0 36); I² = 9%						
Test for overall effect Z = 0 29 (P = 0 77)						
Test for subgroup differences Chi² = 0 26, df = 1 (P = 0 61), I² = 0%						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.2. Comparison 6: Dir t comparison: Long GnRH agonist plus uFSH versus long GnRH gonist plus rFSH, Outcome 2: OHSS

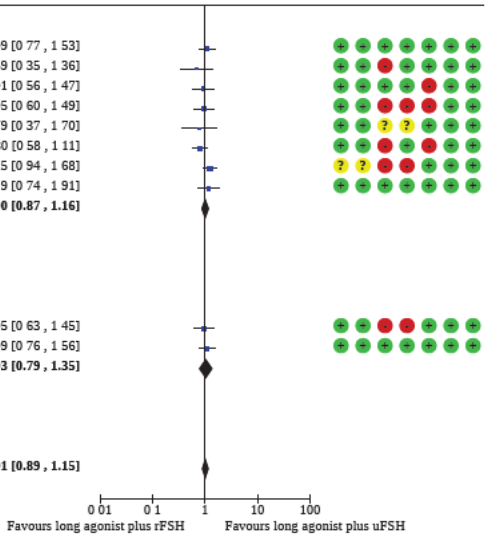
Study or Subgroup	Long agonist plus uFSH Events	Total	Long agonist p rFSH Ev	T al	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Normal response						
Hedon 1995	1	3		60	9 9%	0 51 [0 06 , 4 75]
Lenton 2000	6	7		80	45 1%	0 91 [0 32 , 2 60]
Recombinant Human FSH Study Group 1995	0	63		60		Not estimable
Subtotal (95% CI)		**177**		**200**	**55.0%**	**0.82 [0.32 , 2.12]**
Total events	7		10			
Heterogeneity Tau² = 0 00; Chi² = 0 21, df = 1 (P = 0 64); I² %						
Test for overall effect Z = 0 40 (P = 0 69)						
6.2.2 High response						
Sohrabvand 2012		80	6	80	45 0%	1 17 [0 41 , 3 32]
Subtotal (95% CI)		**80**		**80**	**45.0%**	**1.17 [0.41 , 3.32]**
Total events	7		6			
Heterogeneity Not applicable						
Test for overall effect Z = 0 29 (P = 0 77)						
Total (95% CI)		**257**		**280**	**100.0%**	**0.96 [0.48 , 1.94]**
Total events	14		16			
Heterogeneity Tau² = 0 00; Chi² = 0 45 f = 2 (P = 0); I² = 0%						
Test for overall effect Z = 0 0 (P = 0 9						
Test for subgroup differenc Chi² = 0 23 f = 1 (P = 63), I² = 0%						



Risk of bias legend
(A) Random sequence ratio selection bias)
(B) Allocation concealment tion bias)
(C) Blinding of participants and p nnel (performance bias)
(D) Blinding of outcome assessment (ction bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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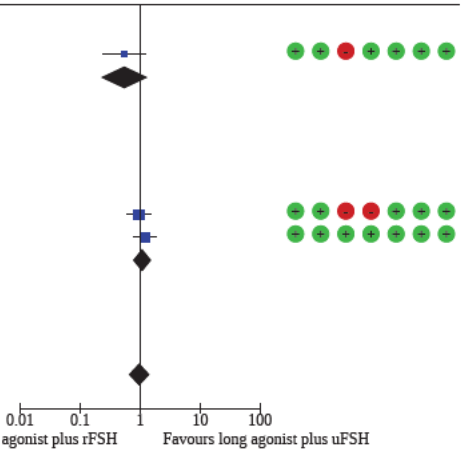
Analysis 6.3. Comparison 6: Direct comparison: Long GnRH agonist plus uFSH versus long GnRH agonist plus rFSH, Outcome 3: Clinical pregnancy



Study or Subgroup	Long agonist plus uFSH Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
6.3.1 Normal response							
Baker 2009	37	76	34	76	14 2%	1 09 [0 77 , 1 53]	+ + + + + + +
Hedon 1995	9	39	20	60	3 6%	0 69 [0 35 , 1 36]	+ + - + + + +
Hoomans 1999	23	85	25	84	7 1%	0 91 [0 56 , 1 47]	+ + + + - + +
Lenton 2000	24	75	27	80	8 1%	0 95 [0 60 , 1 49]	+ + - - - + +
Recombinant Human FSH Study Group 1995	10	63	12	60	2 8%	0 79 [0 37 , 1 70]	+ + ? ? + + +
Schats 2000	50	249	62	247	15 2%	0 80 [0 58 , 1 11]	+ + - + - + +
Selman 2002	61	133	49	134	19 5%	1 25 [0 94 , 1 68]	? ? - - + + +
Selman 2010	23	60	21	65	7 2%	1 19 [0 74 , 1 91]	+ + + + + + +
Subtotal (95% CI)		**780**		**806**	**77.7%**	**1.00 [0.87 , 1.16]**	
Total events	237		250				
Heterogeneity Tau² = 0 00; Chi² = 6 65, df = 7 (P = 0 47); I² = 0%							
Test for overall effect Z = 0 07 (P = 0 95)							
6.3.2 High response							
Aboulghar 2010	21	42	22	42	9 4%	0 95 [0 63 , 1 45]	+ + - - + + +
Sohrabvand 2012	36	80	33	80	12 9%	1 09 [0 76 , 1 56]	+ + + + + + +
Subtotal (95% CI)		**122**		**122**	**22.3%**	**1.03 [0.79 , 1.35]**	
Total events	57		55				
Heterogeneity Tau² = 0 00; Chi² = 0 23, df = 1 (P = 0 63); I² = 0%							
Test for overall effect Z = 0 22 (P = 0 82)							
Total (95% CI)		**902**		**928**	**100.0%**	**.01 [0.89 , 1.15]**	
Total events	294		305				
Heterogeneity Tau² = 0 00; Chi² = 6 89, df = 9 (P = 0 65); I² = 0%							
Test for overall effect Z = 0 16 (P = 0 87)							
Test for subgroup differences Chi² = 0 03, df = 1 (P = 0 87), I² = 0%							

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.4. Comparison 6: Di ect comparison: Long GnRH agonist plus uFSH versus long GnRH agonis pl s rFSH, Outcome 4: Ongoing pregnancy

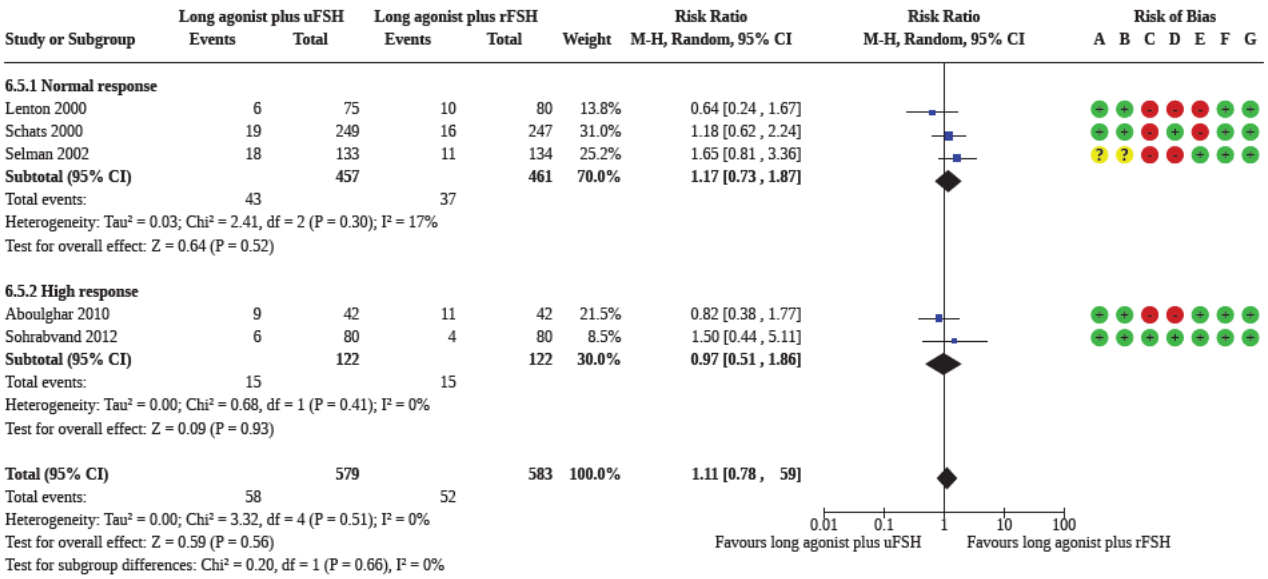


Study or Subgroup	Long agonist plus uFSH Events	Total	Long agonist us rF H Events	T al	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
6.4.1 Normal response							
Hedon 1995	6	39	1	60	16.4%	0.54 [0.23 , 1.26]	+ + - + + + -
Subtotal (95% CI)		**9**		**60**	**16.4%**	**0.54 [0.23 , 1.26]**	
Total events:	6		17				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.43 (P = 0.15)							
6.4.2 High response							
Aboulghar 2010	19	42	20	42	40.8%	0.95 [0.60 , 1.50]	+ + - - + + +
Sohrabvand 2012	29	80	24	80	42.8%	1.21 [0.78 , 1.88]	+ + + + + + +
Subtotal (95% CI)		**122**		**122**	**83.6%**	**1.08 [0.78 , 1.48]**	
Total events:	8		44				
Heterogeneity: Tau² = 0.00; Chi² = 55, df = 1 = 0.46); I² = 0%							
Test for overall effect: Z 0.45 (P 0.65)							
Total (95% CI)		**161**		**182**	**100.0%**	**0.96 [0.67 , 1.39]**	
Total events:	54		61				
Heterogeneity: Tau² = 0 Chi² = 2.80, df = 2 (P = 0.25); I² = 29%							
Test for overall effect: Z = 0.2 (P = 0.83)							
Test for subgroup differences: Chi = 2.23, df = 1 (P = 0.14), I² = 55.2%							

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 6.5. Comparison 6: Direct comparison: Long GnRH agonist plus uFSH versus long GnRH agonist plus rFSH, Outcome 5: Multiple pregnancy

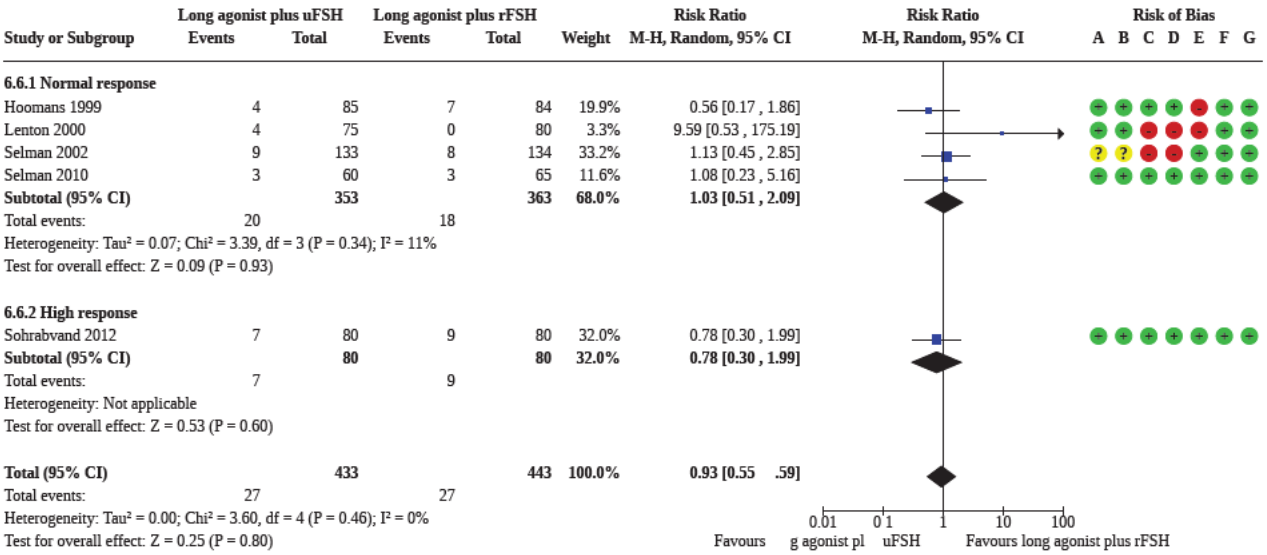


Study or Subgroup	Long agonist plus uFSH Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
6.5.1 Normal response							
Lenton 2000	6	75	10	80	13.8%	0.64 [0.24 , 1.67]	+ + - - - + +
Schats 2000	19	249	16	247	31.0%	1.18 [0.62 , 2.24]	+ + - + - + -
Selman 2002	18	133	11	134	25.2%	1.65 [0.81 , 3.36]	? ? - - + + +
Subtotal (95% CI)		**457**		**461**	**70.0%**	**1.17 [0.73 , 1.87]**	
Total events:	43		37				
Heterogeneity: Tau² = 0.03; Chi² = 2.41, df = 2 (P = 0.30); I² = 17%							
Test for overall effect: Z = 0.64 (P = 0.52)							
6.5.2 High response							
Aboulghar 2010	9	42	11	42	21.5%	0.82 [0.38 , 1.77]	+ + - - + + +
Sohrabvand 2012	6	80	4	80	8.5%	1.50 [0.44 , 5.11]	+ + + + + + +
Subtotal (95% CI)		**122**		**122**	**30.0%**	**0.97 [0.51 , 1.86]**	
Total events:	15		15				
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%							
Test for overall effect: Z = 0.09 (P = 0.93)							
Total (95% CI)		**579**		**583**	**100.0%**	**1.11 [0.78 , 59]**	
Total events:	58		52				
Heterogeneity: Tau² = 0.00; Chi² = 3.32, df = 4 (P = 0.51); I² = 0%							
Test for overall effect: Z = 0.59 (P = 0.56)							
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%							

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

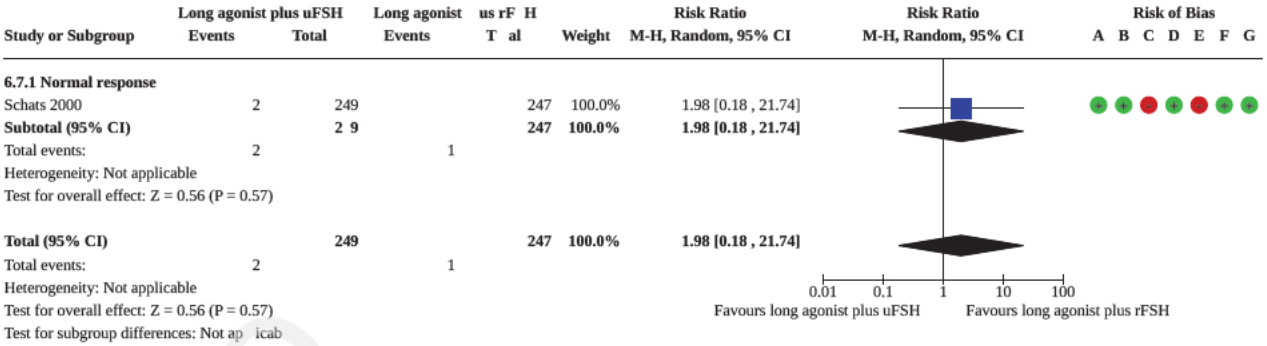
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Analysis 6.6. Comparison 6: Direct comparison: Long GnRH agonist plus uFSH versus long GnRH agonist plus rFSH, Outcome 6: Miscarriage



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

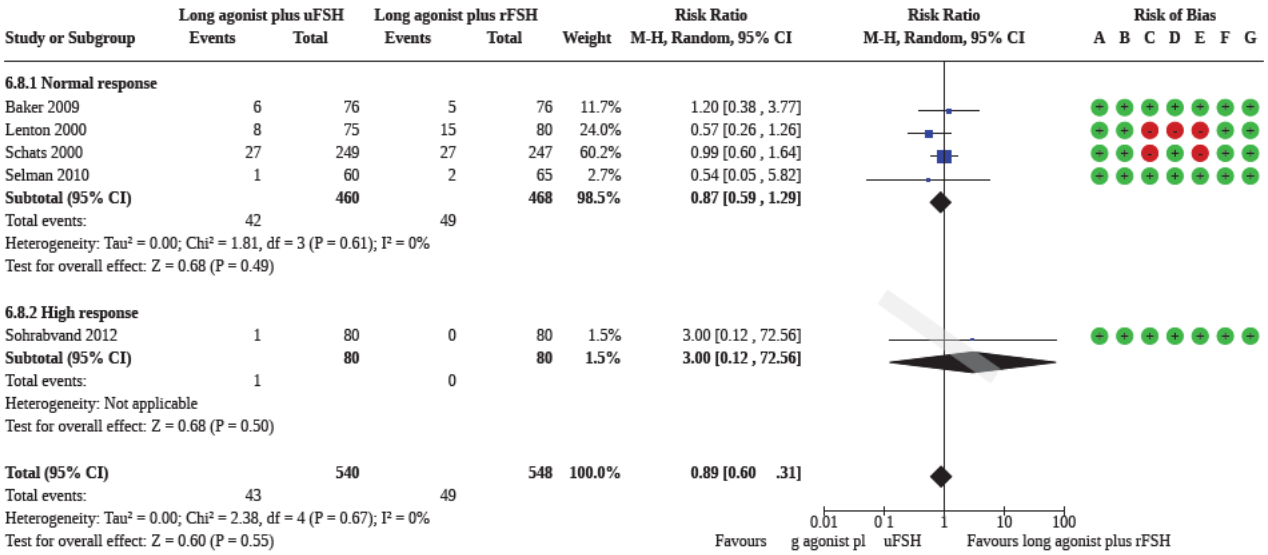
Analysis 6.7. Comparison 6: Direct comparison: Long GnRH agonist plus uFSH versus long GnRH a onist plus rFSH, Outcome 7: Ectopic



Risk of bias legend
(A) Random sequence eneration (sele n b s)
(B) Allocation conc ment (se tion bias)
(C) Blinding of par pants d personnel (performance bias)
(D) Blinding of outcom essment (detection bias)
(E) Incomplete outcome data rition bias)
(F) Selective reporting (reporting as)
(G) Other bias

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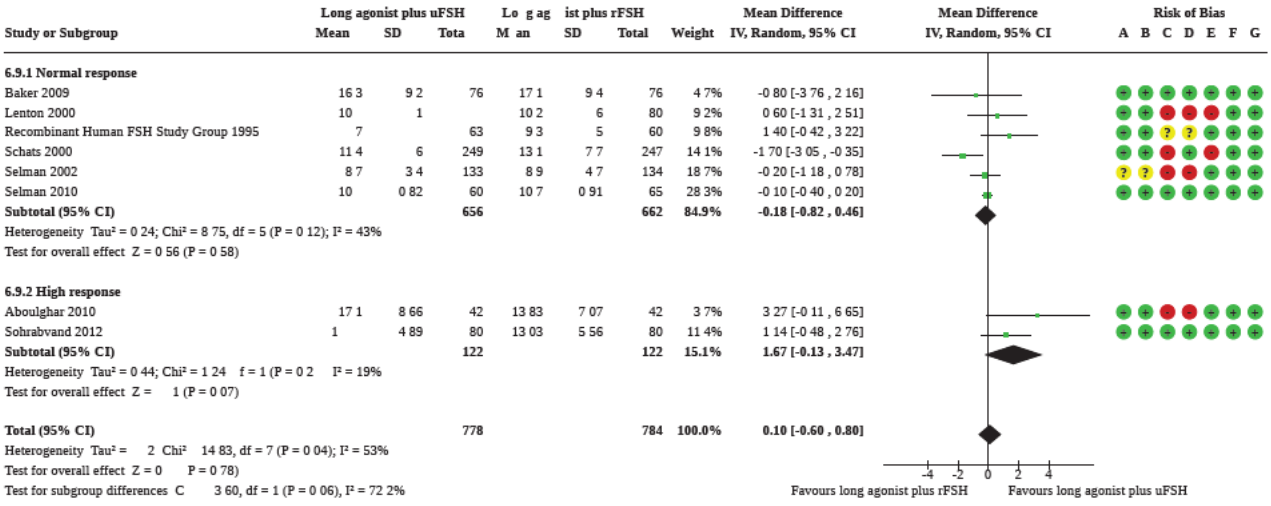
Analysis 6.8. Comparison 6: Direct comparison: Long GnRH agonist plus uFSH versus long GnRH agonist plus rFSH, Outcome 8: Cancellation



Study or Subgroup	Long agonist plus uFSH Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
6.8.1 Normal response							
Baker 2009	6	76	5	76	11.7%	1.20 [0.38 , 3.77]	
Lenton 2000	8	75	15	80	24.0%	0.57 [0.26 , 1.26]	
Schats 2000	27	249	27	247	60.2%	0.99 [0.60 , 1.64]	
Selman 2010	1	60	2	65	2.7%	0.54 [0.05 , 5.82]	
Subtotal (95% CI)		**460**		**468**	**98.5%**	**0.87 [0.59 , 1.29]**	
Total events:	42		49				
Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 3 (P = 0.61); I² = 0%							
Test for overall effect: Z = 0.68 (P = 0.49)							
6.8.2 High response							
Sohrabvand 2012	1	80	0	80	1.5%	3.00 [0.12 , 72.56]	
Subtotal (95% CI)		**80**		**80**	**1.5%**	**3.00 [0.12 , 72.56]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.50)							
Total (95% CI)		**540**		**548**	**100.0%**	**0.89 [0.60 .31]**	
Total events:	43		49				
Heterogeneity: Tau² = 0.00; Chi² = 2.38, df = 4 (P = 0.67); I² = 0%							
Test for overall effect: Z = 0.60 (P = 0.55)							
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%							

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.9. Comparison 6: Di ect comparison: Long GnRH agonist plus uFSH versus long GnRH agoni t lus rFSH, Outcome 9: Oocyte number

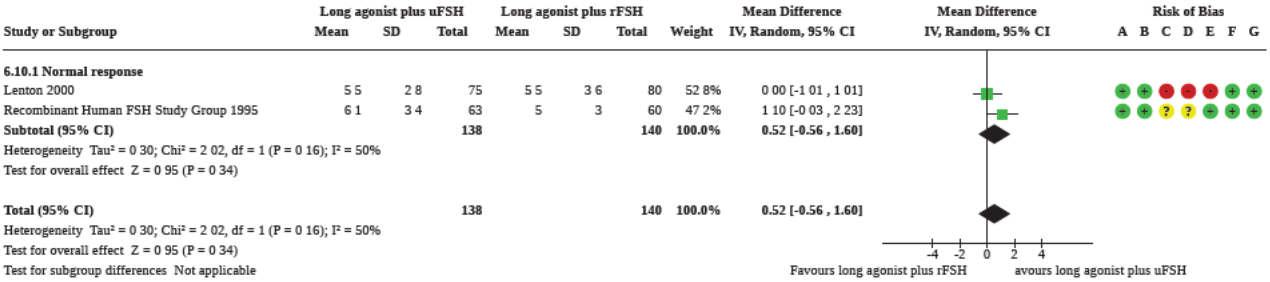


Study or Subgroup	Long agonist plus uFSH Mean	SD	Tota	Lo g ag M an	ist plus rFSH SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
6.9.1 Normal response									
Baker 2009	16 3	9 2	76	17 1	9 4	76	4 7%	-0 80 [-3 76 , 2 16]	
Lenton 2000	10	1		10 2	6	80	9 2%	0 60 [-1 31 , 2 51]	
Recombinant Human FSH Study Group 1995	7		63	9 3	5	60	9 8%	1 40 [-0 42 , 3 22]	
Schats 2000	11 4	6	249	13 1	7 7	247	14 1%	-1 70 [-3 05 , -0 35]	
Selman 2002	8 7	3 4	133	8 9	4 7	134	18 7%	-0 20 [-1 18 , 0 78]	
Selman 2010	10	0 82	60	10 7	0 91	65	28 3%	-0 10 [-0 40 , 0 20]	
Subtotal (95% CI)			**656**			**662**	**84.9%**	**-0.18 [-0.82 , 0.46]**	
Heterogeneity Tau² = 0 24; Chi² = 8 75, df = 5 (P = 0 12); I² = 43%									
Test for overall effect Z = 0 56 (P = 0 58)									
6.9.2 High response									
Aboulghar 2010	17 1	8 66	42	13 83	7 07	42	3 7%	3 27 [-0 11 , 6 65]	
Sohrabvand 2012	1	4 89	80	13 03	5 56	80	11 4%	1 14 [-0 48 , 2 76]	
Subtotal (95% CI)			**122**			**122**	**15.1%**	**1.67 [-0.13 , 3.47]**	
Heterogeneity Tau² = 0 44; Chi² = 1 24 f = 1 (P = 0 2 I² = 19%									
Test for overall effect Z = 1 (P = 0 07)									
Total (95% CI)			**778**			**784**	**100.0%**	**0.10 [-0.60 , 0.80]**	
Heterogeneity Tau² = 2 Chi² 14 83, df = 7 (P = 0 04); I² = 53%									
Test for overall effect Z = 0 P = 0 78)									
Test for subgroup differences C 3 60, df = 1 (P = 0 06), I² = 72 2%									

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

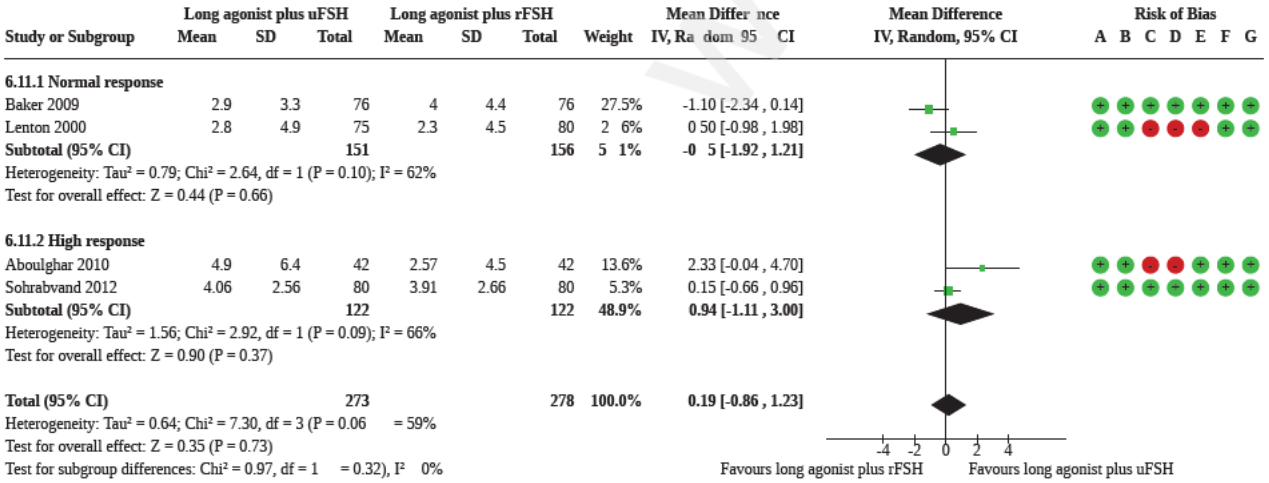
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Analysis 6.10. Comparison 6: Direct comparison: Long GnRH agonist plus uFSH versus long GnRH agonist plus rFSH, Outcome 10: Cleavage embryo number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.11. Comparison 6: Direct comparison: L ng nRH agonist plus uFSH versus long GnRH agonist plus rFSH, Outcome 11: Frozen embryo number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (p formance bias)
(D) Blinding of outcome assessment (detec bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 7. Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Live birth	1	731	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.92, 1.53]
7.1.1 Normal response	1	731	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.92, 1.53]

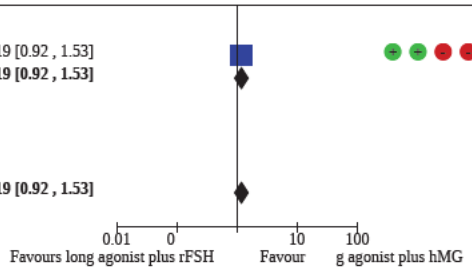
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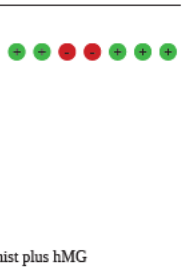
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 OHSS	4	2820	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.67, 1.71]
7.2.1 Normal response	4	2820	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.67, 1.71]
7.3 Clinical pregnancy	2	1512	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.99, 1.43]
7.3.1 Normal response	2	1512	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.99, 1.43]
7.4 Ongoing pregnancy	4	2181	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.97, 1.32]
7.4.1 Normal response	4	2181	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.97, 1.32]
7.5 Multiple pregnancy	2	821	Risk Ratio (M-H, Random, 95% I)	1.13 [0.69, 1.86]
7.5.1 Normal response	2	821	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.69, 1.86]
7.6 Miscarriage	2	1512	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.67, 1.30]
7.6.1 Normal response	2	1512	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.67, 1.30]
7.7 Cancellation	2	1410	Risk Ratio M-H, Random, 95% CI)	0.89 [0.67, 1.20]
7.7.1 Normal response	2	1410	Risk Rat o (M-H, Random, 95% CI)	0.89 [0.67, 1.20]
7.8 Oocyte number	2	1410	Mea Difference (IV, Random, 95% CI)	-1.24 [-2.42, -0.07]
7.8.1 Normal response	2	1410	Mean Difference (IV, Random, 95% CI)	-1.24 [-2.42, -0.07]
7.9 Frozen embryo number	1	731	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.51, 0.31]
7.9.1 Normal response	1	73	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.51, 0.31]

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Analysis 7.1. Comparison 7: Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH, Outcome 1: Live birth

Study or Subgroup	Long agonist plus hMG Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Normal response						
Andersen 2006	96	363	82	368	100.0%	1.19 [0.92 , 1.53]
Subtotal (95% CI)		**363**		**368**	**100.0%**	**1.19 [0.92 , 1.53]**
Total events:	96		82			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
Total (95% CI)		**363**		**368**	**100.0%**	**1.19 [0.92 , 1.53]**
Total events:	96		82			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Not applicable						

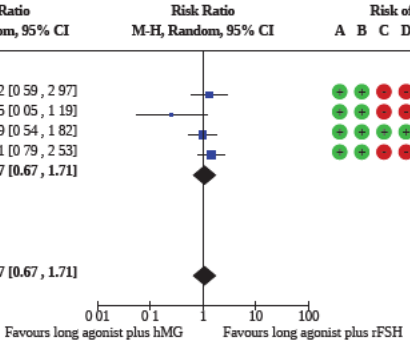




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.2. Comparison 7: Direct co parison: Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH, Outcome 2: OHSS

Study or Subgroup	Long agonist plus hMG Events	Total	Long agonist plus rFSH Events	Tota	W ght	Risk Ratio M-H, Random, 95% CI
7.2.1 Normal response						
Andersen 2006	13	363	10	36	%	1 32 [0 59 , 2 97]
Hompes 2008	2	312	8	317	8 3%	0 25 [0 05 , 1 19]
Melo 2010	19	333	20	3	33 4%	0 99 [0 54 , 1 82]
The European and Israeli Study Group 2002	26	395	18	386	35 0%	1 41 [0 79 , 2 53]
Subtotal (95% CI)		**1403**		**1417**	**100.0%**	**1.07 [0.67 , 1.71]**
Total events	60		56			
Heterogeneity Tau² = 0 08; Chi² = 4 51, df = 3 (P = 0 21); I² = 33%						
Test for overall effect Z = 0 28 (P = 0 78)						
Total (95% CI)		**403**		**1417**	**100.0%**	**1.07 [0.67 , 1.71]**
Total events	60		6			
Heterogeneity Tau² = 0 08; Chi² = 4 51, df = 3 (P = 0 21); I² = 33%						
Test for overall effect Z = 0 28 (P = 0 78)						
Test for subgroup differences Not applicable						

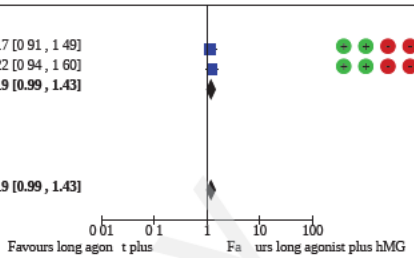


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 7.3. Comparison 7: Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH, Outcome 3: Clinical pregnancy

Study or Subgroup	Long agonist plus hMG Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.3.1 Normal response						
Andersen 2006	100	363	87	368	53 7%	1 17 [0 91 , 1 49]
The European and Israeli Study Group 2002	95	395	76	386	46 3%	1 22 [0 94 , 1 60]
Subtotal (95% CI)		**758**		**754**	**100.0%**	**1.19 [0.99 , 1.43]**
Total events	195		163			
Heterogeneity Tau² = 0 00; Chi² = 0 06, df = 1 (P = 0 80); I² = 0%						
Test for overall effect Z = 1 88 (P = 0 06)						
Total (95% CI)		**758**		**754**	**100.0%**	**1.19 [0.99 , 1.43]**
Total events	195		163			
Heterogeneity Tau² = 0 00; Chi² = 0 06, df = 1 (P = 0 80); I² = 0%						
Test for overall effect Z = 1 88 (P = 0 06)						
Test for subgroup differences Not applicable						

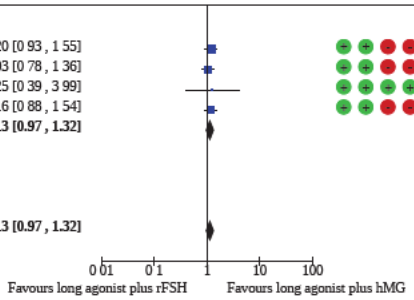




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.4. Comparison 7: Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH, Out ome 4: Ongoing pregnancy

Study or Subgroup	Long agonist plus hMG Events	Total	Long agonist plus rFSH Events	Total	W	M-	Risk Ratio Random, 95% CI
7.4.1 Normal response							
Andersen 2006	97	363	82	368	36 3		1 20 [0 93 , 1 55]
Hompes 2008	77	312	7	317	31 2%		1 03 [0 78 , 1 36]
Ng 2001	5	20	4		1 8%		1 25 [0 39 , 3 99]
The European and Israeli Study Group 2002	87	395	73	386	30 8%		1 16 [0 88 , 1 54]
Subtotal (95% CI)		**1090**		**1**	**100.0%**		**1.13 [0.97 , 1.32]**
Total events	266		235				
Heterogeneity Tau² = 0 00; Chi² = 0 72, df = 3 (P = 0 87); I² = 0%							
Test for overall effect Z = 1 60 (P = 0 11)							
Total (95% CI)		**1090**		**1091**	**100.0%**		**1.13 [0.97 , 1.32]**
Total events	266		23				
Heterogeneity Tau² = 0 00; Chi² = 0 72, df = 3 (P = 0 87); I² = 0%							
Test for overall effect Z = 1 60 (P = 0 11)							
Test for subgroup differences Not applicable							



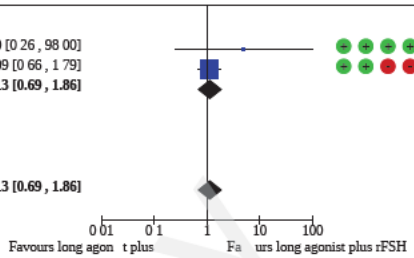


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance b
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 7.5. Comparison 7: Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH, Outcome 5: Multiple pregnancy

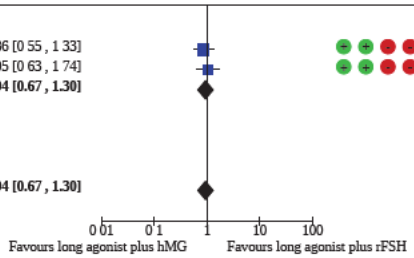
Study or Subgroup	Long agonist plus hMG Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.5.1 Normal response						
Ng 2001	2	20	0	20	2 8%	5 00 [0 26 , 98 00]
The European and Israeli Study Group 2002	30	395	27	386	97 2%	1 09 [0 66 , 1 79]
Subtotal (95% CI)		**415**		**406**	**100.0%**	**1.13 [0.69 , 1.86]**
Total events	32		27			
Heterogeneity Tau² = 0 00; Chi² = 0 99, df = 1 (P = 0 32); I² = 0%						
Test for overall effect Z = 0 49 (P = 0 62)						
Total (95% CI)		**415**		**406**	**100.0%**	**1.13 [0.69 , 1.86]**
Total events	32		27			
Heterogeneity Tau² = 0 00; Chi² = 0 99, df = 1 (P = 0 32); I² = 0%						
Test for overall effect Z = 0 49 (P = 0 62)						
Test for subgroup differences Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.6. Comparison 7: Direct comp rison: Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH Outcome 6: Miscarriage

Study or Subgroup	Long agonist plus hMG Events	Total	Long agonist plus rFSH Events	Total	W	M-	Risk Ratio Random, 95% CI
7.6.1 Normal response							
Andersen 2006	33	363	39	368	56 8		0 86 [0 55 , 1 33]
The European and Israeli Study Group 2002	29	395	7	386	43 2%		1 05 [0 63 , 1 74]
Subtotal (95% CI)		**758**			**100 0**		**0.94 [0.67 , 1.30]**
Total events	62		66				
Heterogeneity Tau² = 0 00; Chi² = 0 35, df = 1 (P = 0 55); I² = 0%							
Test for overall effect Z = 0 39 (P = 0 70)							
Total (95% CI)		**758**		**754**	**100.0%**		**0.94 [0.67 , 1.30]**
Total events	62		66				
Heterogeneity Tau² = 0 00; Chi² = 0 35, df = 1 (P = 0 55); I² = 0%							
Test for overall effect Z = 0 39 (P = 0 70)							
Test for subgroup differences Not applicable							

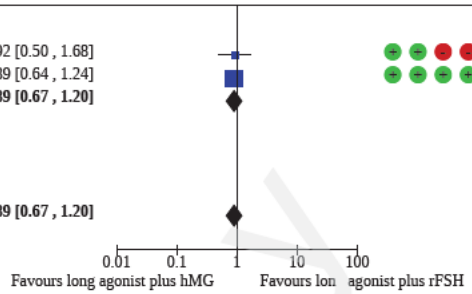


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance b)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 7.7. Comparison 7: Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH, Outcome 7: Cancellation

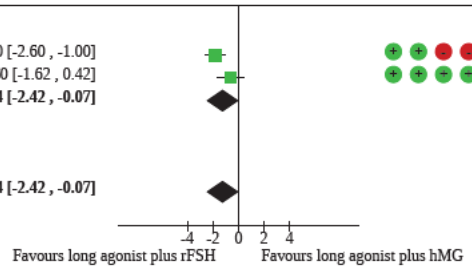
Study or Subgroup	Long agonist plus hMG Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
7.7.1 Normal response								
Andersen 2006	19	363	21	368	23.5%	0.92 [0.50 , 1.68]		
Melo 2010	53	333	62	346	76.5%	0.89 [0.64 , 1.24]		
Subtotal (95% CI)		**696**		**714**	**100.0%**	**0.89 [0.67 , 1.20]**		
Total events:	72		83					
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%								
Test for overall effect: Z = 0.74 (P = 0.46)								
Total (95% CI)		**696**		**714**	**100.0%**	**0.89 [0.67 , 1.20]**		
Total events:	72		83					
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%								
Test for overall effect: Z = 0.74 (P = 0.46)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.8. Comparison 7: Direct compariso Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH Outcome 8: Oocyte number

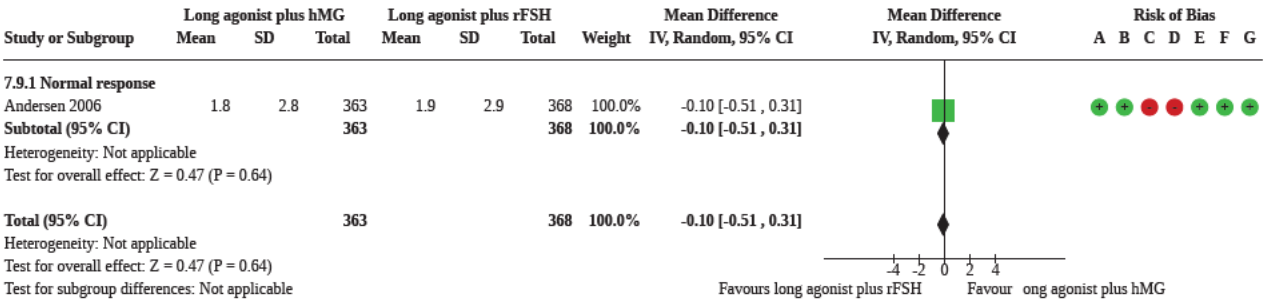
Study or Subgroup	Long agonist plus hMG Mean	SD	Total	Long agonist plus rFSH Mean	SD	Total	We ht	Mean Difference IV, Ra dom, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
7.8.1 Normal response										
Andersen 2006	10	5.4	363	11.8	5.7	3 8	53.6	-1.80 [-2.60 , -1.00]		
Melo 2010	18.7	6.4	333	19.3	7.2	346	46.4%	-0.60 [-1.62 , 0.42]		
Subtotal (95% CI)			**696**			**714**	**00.0%**	**-1.24 [-2.42 , -0.07]**		
Heterogeneity: Tau² = 0.50; Chi² = 3.26, df = 1 (P = 0.07); I² = 69%										
Test for overall effect: Z = 2.08 (P = 0.04)										
Total (95% CI)			**696**			**4**	**100.0%**	**-1.24 [-2.42 , -0.07]**		
Heterogeneity: Tau² = 0.50; Chi² = 3.26, df = 1 (P = 0.07); I² = 69%										
Test for overall effect: Z = 2.08 (P = 0.04)										
Test for subgroup differences: Not applicable										



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 7.9. Comparison 7: Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH, Outcome 9: Frozen embryo number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

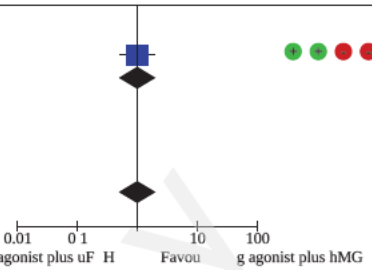
Comparison 8. Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus uFSH

Outcome or subgroup title	No. of studies	No. of participants	Statis ca method	Effect size
8.1 Live birth	1	111	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.51, 1.89]
8.1.1 Normal response	1	111	isk Ratio (M-H, Random, 95% CI)	0.98 [0.51, 1.89]
8.2 Multiple pregnancy	1	111	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.19, 3.37]
8.2.1 Normal response	1	111	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.19, 3.37]
8.3 Miscarriage	1	11	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.19, 1.94]
8.3.1 Normal response	1	11	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.19, 1.94]
8.4 Ectopic	1	111	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.85]
8.4.1 Normal response	1	111	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.85]
8.5 Cancellation	1	111	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.19, 3.37]
8.5.1 Normal response	1	111	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.19, 3.37]
8.6 Oocyte numb r	1	111	Mean Difference (IV, Random, 95% CI)	-3.20 [-3.52, -2.88]
8.6.1 Normal respons	1	111	Mean Difference (IV, Random, 95% CI)	-3.20 [-3.52, -2.88]

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Analysis 8.1. Comparison 8: Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus uFSH, Outcome 1: Live birth

Study or Subgroup	Long agonist plus hMG Events	Total	Long agonist plus uFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Normal response						
Miron 1998	13	54	14	57	100.0%	0.98 [0.51 , 1.89]
Subtotal (95% CI)		**54**		**57**	**100.0%**	**0.98 [0.51 , 1.89]**
Total events:	13		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95% CI)		**54**		**57**	**100.0%**	**0.98 [0.51 , 1.89]**
Total events:	13		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
Test for subgroup differences: Not applicable						

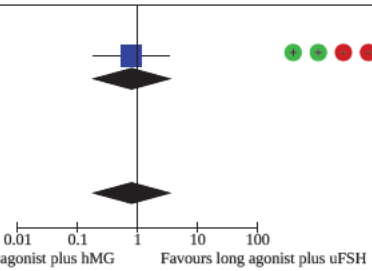




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 8.2. Comparison 8: Direct comp rison: Long GnRH agonist plus hMG versus long GnRH agonist plus uFSH, Outcome 2: Multiple pregnancy

Study or Subgroup	Long agonist plus hMG Events	Total	Long agonist plus uFSH Events	Total	Weigh	Risk Ratio M-H Ra dom, 95% CI
8.2.1 Normal response						
Miron 1998	3	54	4	57	100 0%	0.79 [0.19 , 3.37]
Subtotal (95% CI)		**54**		**57**	**100.0%**	**0.79 [0.19 , 3.37]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
Total (95% CI)		**54**		**57**	**100.0%**	**0.79 [0.19 , 3.37]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
Test for subgroup differences: Not applicable						

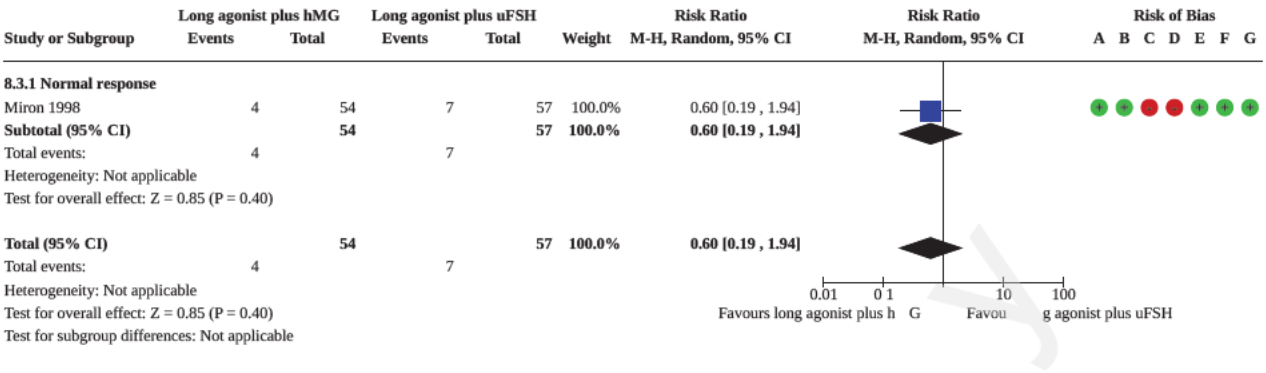




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

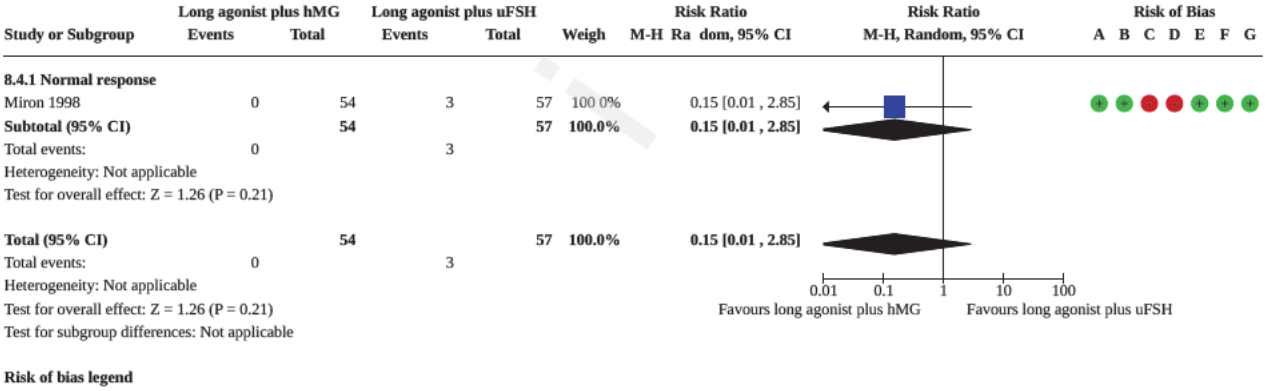
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Analysis 8.3. Comparison 8: Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus uFSH, Outcome 3: Miscarriage



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

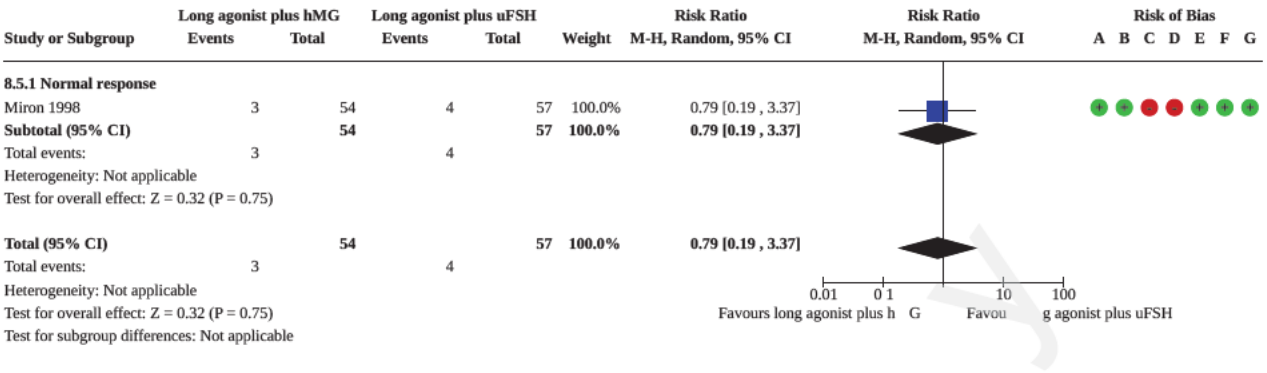
Analysis 8.4. Comparison 8: Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus uFSH, Outcome 4: Ectopic



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

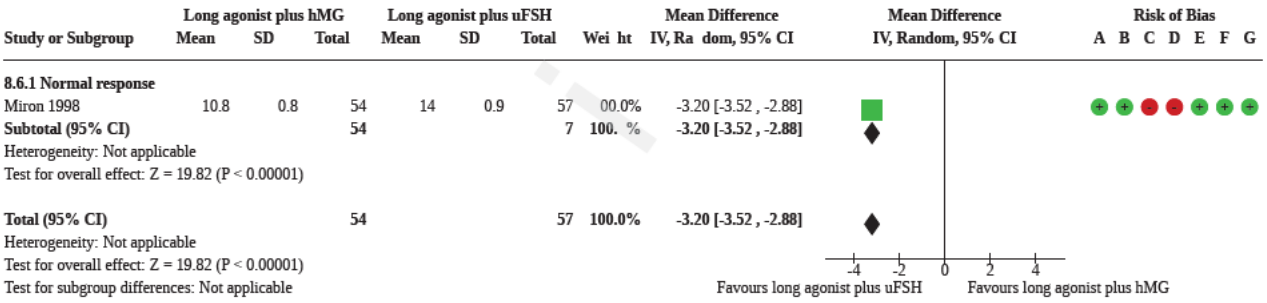
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Analysis 8.5. Comparison 8: Direct comparison: Long GnRH agonist plus hMG versus long GnRH agonist plus uFSH, Outcome 5: Cancellation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 8.6. Comparison 8: Direct comp rison: Long GnRH agonist plus hMG versus long GnRH agonist plus uFSH, Outcome 6: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (perfor ce bia
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

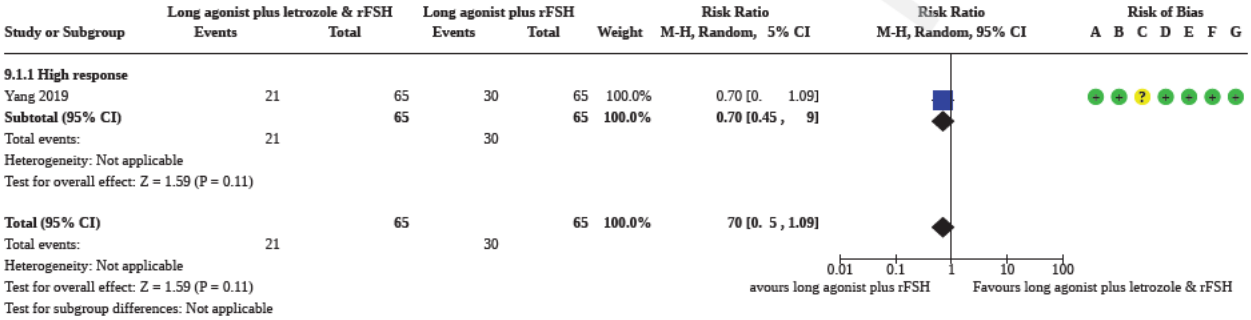
Comparison 9. Direct c mpari on: Long GnRH agonist plus letrozole & rFSH versus long GnRH agonist plus rFSH

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
9.1 Live birth	1	130	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.45, 1.09]
9.1.1 High response	1	130	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.45, 1.09]
9.2 OHSS	1	130	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.03]
9.2.1 High response	1	130	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.03]

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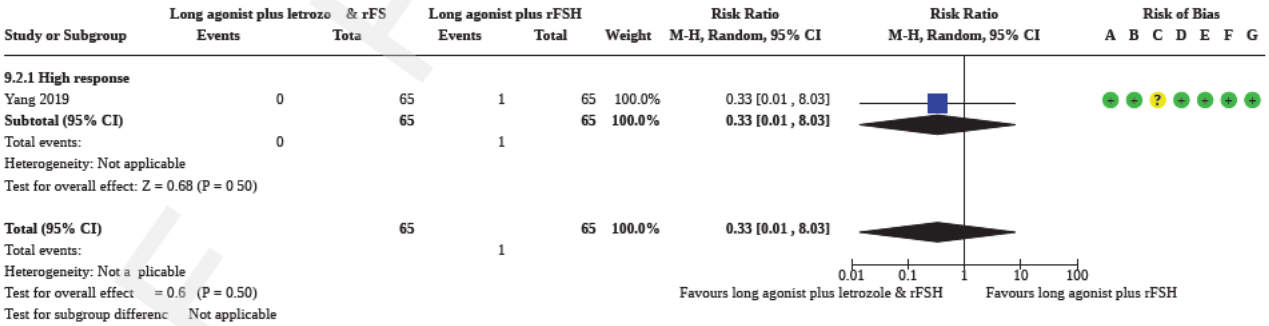
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3 Clinical pregnancy	1	130	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.08]
9.3.1 High response	1	130	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.08]
9.4 Miscarriage	1	130	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.26, 3.83]
9.4.1 High response	1	130	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.26, 3.83]

Analysis 9.1. Comparison 9: Direct comparison: Long GnRH agon st plus letrozole & rFSH versus long GnRH agonist plus rFSH, Outcome 1 Live birth



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

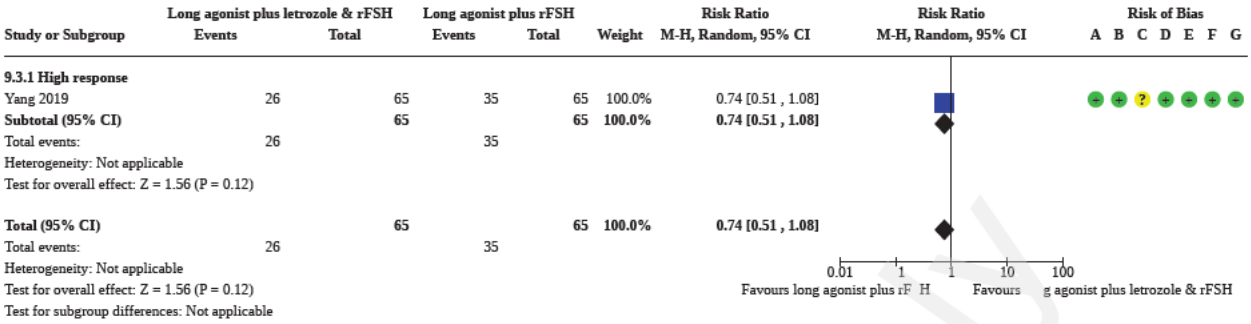
Analysis 9.2. Comparison 9: Direct comparison: Long GnRH agonist plus letrozole & rFSH versu long GnRH agonist plus rFSH, Outcome 2: OHSS



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

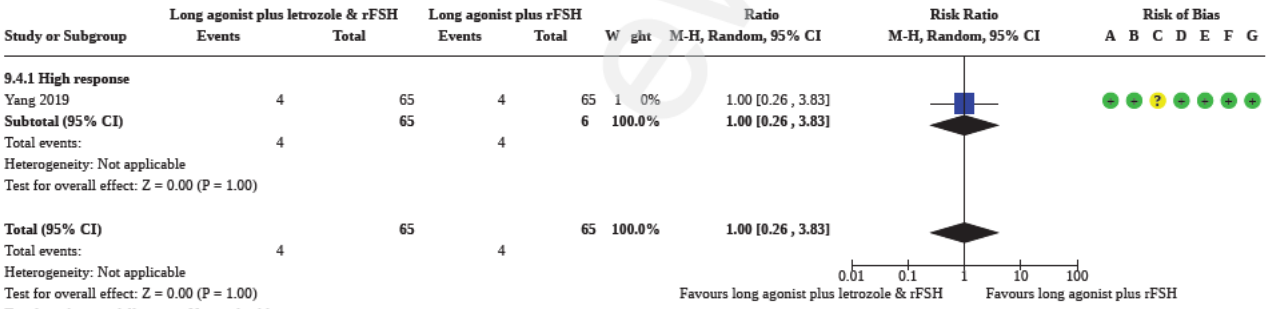
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Analysis 9.3. Comparison 9: Direct comparison: Long GnRH agonist plus letrozole & rFSH versus long GnRH agonist plus rFSH, Outcome 3: Clinical pregnancy



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 9.4. Comparison 9: Direct comparison: Long GnRH agonist plus letrozole & rFSH versus long GnRH agonist plus rF H, Outcome 4: Miscarriage



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performanc ias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 10. Direct ompar son: Long GnRH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
10.1 Live birth	4	1284	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.62, 1.50]
10.1.1 Normal response	3	345	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.48, 2.30]
10.1.2 Low response	1	939	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.63, 1.30]
10.2 OHSS	2	301	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.90]

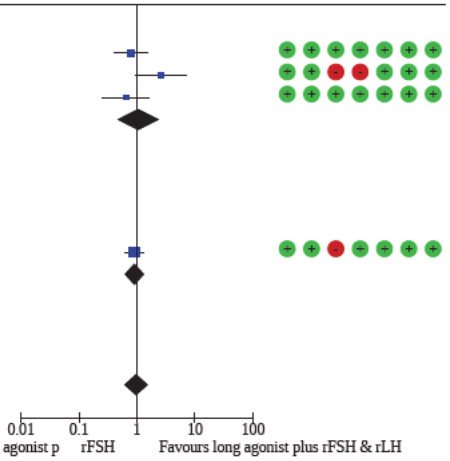
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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2.1 Normal response	2	301	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.90]
10.3 Clinical pregnancy	8	2472	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.06]
10.3.1 Normal response	6	1289	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.78, 1.13]
10.3.2 Low response	2	1183	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.66, 1.14]
10.4 Ongoing pregnancy	4	1839	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.20]
10.4.1 Normal response	1	526	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.24]
10.4.2 Low response	3	1313	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.78, 1.35]
10.5 Multiple pregnancy	4	944	Risk Ratio M-H, Random, 95% CI)	1.13 [0.63, 2.02]
10.5.1 Normal response	4	944	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.63, 2.02]
10.6 Miscarriage	9	2602	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.52, 0.92]
10.6.1 Normal response	6	1289	Ri k Ratio (M-H, Random, 95% CI)	0.88 [0.56, 1.40]
10.6.2 Low response	3	1313	Risk Ra io (M-H, Random, 95% CI)	0.60 [0.42, 0.85]
10.7 Ectopic	1	939	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.43]
10.7.1 Low response	1	939	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.43]
10.8 Cancellation	6	2084	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.69, 1.31]
10.8.1 Normal response	3	7 1	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.25, 1.89]
10.8.2 Low response	3	1313	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.68, 1.43]
10.9 Oocyte number	8	2358	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.98, 0.74]
10.9.1 Normal response	6	1289	Mean Difference (IV, Random, 95% CI)	-0.81 [-1.33, -0.28]
10.9.2 Low response	2	1069	Mean Difference (IV, Random, 95% CI)	1.24 [-1.89, 4.38]
10.10 Frozen embryo number	1	526	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.48, 0.28]
10.10.1 Normal re ponse		526	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.48, 0.28]

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Analysis 10.1. Comparison 10: Direct comparison: Long GnRH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH, Outcome 1: Live birth

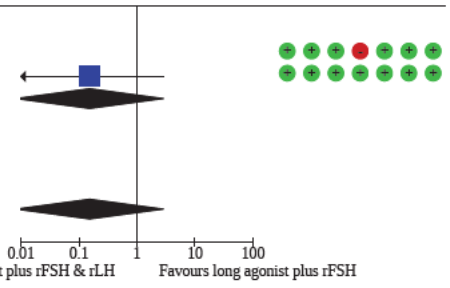
Study or Subgroup	Long agonist plus rFSH & rLH Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
10.1.1 Normal response								
Lahoud 2017	10	43	17	57	25.2%	0.78 [0.40 , 1.53]		
Matorras 2009	12	63	5	68	15.1%	2.59 [0.97 , 6.94]		
Tarlatzis 2006	6	55	10	59	16.1%	0.64 [0.25 , 1.65]		
Subtotal (95% CI)		**161**		**184**	**56.4%**	**1.05 [0.48 , 2.30]**		
Total events:	28		32					
Heterogeneity: Tau² = 0.29; Chi² = 4.98, df = 2 (P = 0.08); I² = 60%								
Test for overall effect: Z = 0.12 (P = 0.90)								
10.1.2 Low response								
Humaidan 2017	49	462	56	477	43.6%	0.90 [0.63 , 1.30]		
Subtotal (95% CI)		**462**		**477**	**43.6%**	**0.90 [0.63 , 1.30]**		
Total events:	49		56					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.55 (P = 0.58)								
Total (95% CI)		**623**		**661**	**100.0%**	**0.97 [0.62 , 1 50]**		
Total events:	77		88					
Heterogeneity: Tau² = 0.08; Chi² = 5.04, df = 3 (P = 0.17); I² = 40%								
Test for overall effect: Z = 0.15 (P = 0.88)								
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 10.2. Comparison 10: irect comparison: Long GnRH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH, Outcome 2: OHSS

Study or Subgroup	Long agonist plus rFSH & rLH Events	Total	Long agonist plus rFSH Events	al	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
10.2.1 Normal response								
Fabregues 2011	0	125	0	62		Not estimable		
Tarlatzis 2006	0	55	3	59	100.0%	0.15 [0.01 , 2.90]		
Subtotal (95% CI)		**180**		**121**	**100.0%**	**0.15 [0.01 , 2.90]**		
Total events:	0							
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.25 (P = 0.21)								
Total (95% CI)		**18**		**121**	**100.0%**	**0.15 [0.01 , 2.90]**		
Total events:	0		3					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.25 (P = 0.21)								
Test for subgroup differences: Not applicable								

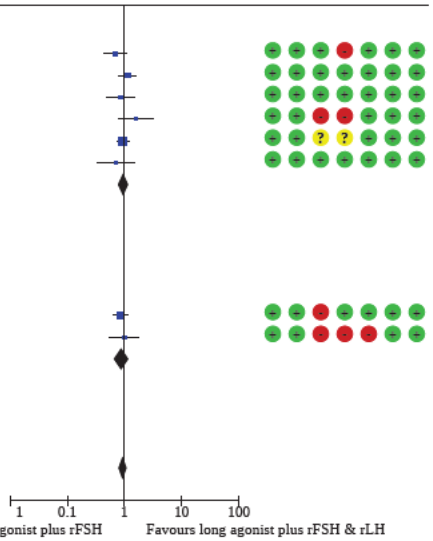


Risk of bias legend
(A) Random sequence generation (s ection bias)
(B) Allocation concealm (selectio bias)
(C) Blinding of partici nts and personn rmance bias)
(D) Blinding of out me assess nt (detection bias)
(E) Incomplete outco data ttrition bias)
(F) Selective reporting (r ing bias)
(G) Other bias

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Analysis 10.3. Comparison 10: Direct comparison: Long GnRH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH, Outcome 3: Clinical pregnancy

Study or Subgroup	Long agonist plus rFSH & rLH Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
10.3.1 Normal response							
Fabregues 2011	31	125	22	62	9.7%	0.70 [0.44 , 1.10]	+ + + - + + +
Humaidan 2004	42	116	37	115	15.6%	1.13 [0.79 , 1.61]	+ + + + + + +
Lahoud 2017	13	43	20	57	6.1%	0.86 [0.48 , 1.53]	+ + + + + + +
Matorras 2009	16	63	11	68	4.2%	1.57 [0.79 , 3.12]	+ + - - + + +
Nyboe Andersen 2008	83	265	88	261	33.0%	0.93 [0.73 , 1.19]	+ + ? ? + + +
Tarlatzis 2006	9	55	14	59	3.5%	0.69 [0.32 , 1.46]	+ + + + + + +
Subtotal (95% CI)		**667**		**622**	**72.1%**	**0.94 [0.78 , 1.13]**	
Total events:	194		192				
Heterogeneity: Tau² = 0.01; Chi² = 5.50, df = 5 (P = 0.36); I² = 9%							
Test for overall effect: Z = 0.66 (P = 0.51)							
10.3.2 Low response							
Humaidan 2017	65	462	80	477	22.1%	0.84 [0.62 , 1.13]	+ + - + + + +
Musters 2012	18	116	20	128	5.8%	0.99 [0.55 , 1.78]	+ + - - - + +
Subtotal (95% CI)		**578**		**605**	**27.9%**	**0.87 [0.66 , 1.14]**	
Total events:	83		100				
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%							
Test for overall effect: Z = 1.03 (P = 0.30)							
Total (95% CI)		**1245**		**1227**	**100.0%**	**0.92 [0 80 , 1.06]**	
Total events:	277		292				
Heterogeneity: Tau² = 0.00; Chi² = 5.99, df = 7 (P = 0.54); I² = 0%							
Test for overall effect: Z = 1.15 (P = 0.25)							
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%							



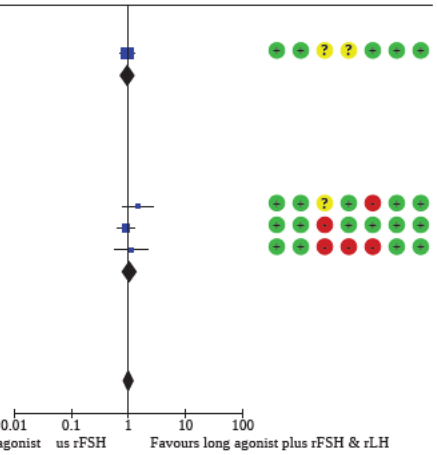
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 10.4. Comparison 10: Direct comparison: Long GnRH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH, Outcome 4: Ongoing pregnancy

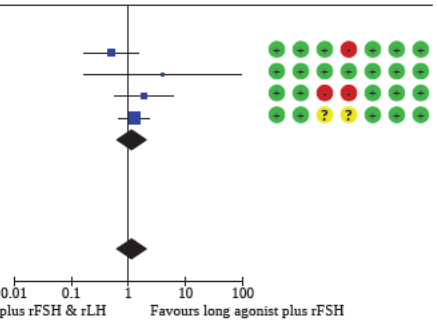
Study or Subgroup	Long agonist plus rFSH & rLH Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
10.4.1 Normal response							
Nyboe Andersen 2008	72	265	75	261	50.7%	0.95 [0.72 , 1.24]	+ + ? ? + + +
Subtotal (95% CI)		**265**		**261**	**50.7%**	**0.95 [0.72 , 1.24]**	
Total events:	72		75				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.40 (P = 0.69)							
10.4.2 Low response							
De Placido 2005	19	65	13	65	10.1%	1.46 [0.79 , 2.71]	+ + ? + - + +
Humaidan 2017	51	462	59	477	30.8%	0.89 [0.63 , 1.27]	+ + - + + + +
Musters 2012	15	116	15	128	8.5%	1.10 [0.56 , 2.16]	+ + - - - + +
Subtotal (95% CI)		**643**		**670**	**49.3%**	**1.02 [0.78 , 1.35]**	
Total events:	85		87				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.92$, df = 2 (P = 0.38); $I^2 = 0\%$							
Test for overall effect: Z = 0.16 (P = 0.87)							
Total (95% CI)		**908**		**931**	**100.0%**	**0.98 [0.81 , 1.20]**	
Total events:	157		162				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.07$, df = 3 (P = 0.56); $I^2 = 0\%$							
Test for overall effect: Z = 0.17 (P = 0.87)							
Test for subgroup differences: $Chi^2 = 0.16$, df = 1 (P = 0.69), $I^2 = 0\%$							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 10.5. Comparison 10: D rect c mparison: Long GnRH agonist plus rFSH & rLH versus long GnRH ago ist plus rFSH, Outcome 5: Multiple pregnancy

Study or Subgroup	Long agonist plus rFSH & rLH Events	Total	Long agonist plus H Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
10.5.1 Normal response							
Fabregues 2011	6	125	6	62	23.7%	0.50 [0.17 , 1.48]	+ + + - + + +
Lahoud 2017	1	43	0	57	3.3%	3.95 [0.17 , 94.76]	+ + + + + + +
Matorras 2009	7	63	4	68	20.8%	1.89 [0.58 , 6.15]	+ + - - + + +
Nyboe Andersen 2008	20		16	261	52.2%	1.23 [0.65 , 2.32]	+ + ? ? + + +
Subtotal (95% CI)		**496**		**448**	**100.0%**	**1.13 [0.63 , 2.02]**	
Total events:	34		26				
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 3.59$, df = 3 (P = 1); I^2 = %							
Test for overall effect: Z = 0.40 (P = 0.69)							
Total (95% CI)		**496**		**448**	**100.0%**	**1.13 [0.63 , 2.02]**	
Total events:	34		26				
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 3.59$, df = 3 P = 0.31); $I^2 = 17\%$							
Test for overall effect: Z = 0.40 (P = 0.69)							
Test for subgroup differences: Not appli							

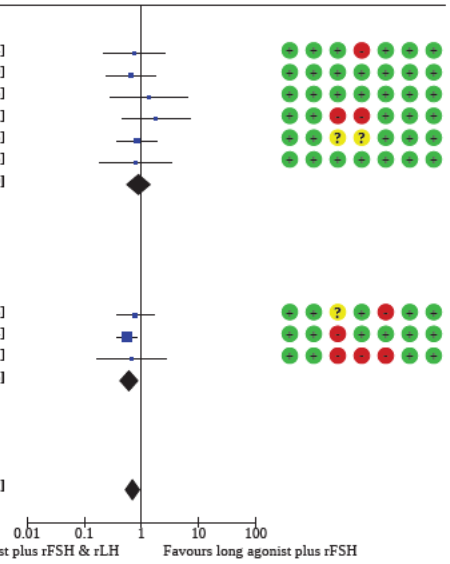


Risk of bias legend
(A) Random sequence ge ration (sel ion bias)
(B) Allocation conceal ent (selection bias)
(C) Blinding of part pants and ersonnel (performance bias)
(D) Blinding of outcom ass sment (detection bias)
(E) Incomplete outcome da (attrition bias)
(F) Selective reporting (reporting ias)
(G) Other bias

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Analysis 10.6. Comparison 10: Direct comparison: Long GnRH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH, Outcome 6: Miscarriage

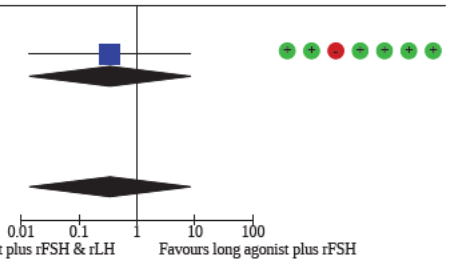
Study or Subgroup	Long agonist plus rFSH & rLH Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10.6.1 Normal response						
Fabregues 2011	6	125	4	62	5.2%	0.74 [0.22 , 2.54]
Humaidan 2004	6	116	9	115	7.8%	0.66 [0.24 , 1.80]
Lahoud 2017	3	43	3	57	3.3%	1.33 [0.28 , 6.25]
Matorras 2009	5	63	3	68	4.1%	1.80 [0.45 , 7.22]
Nyboe Andersen 2008	11	265	13	261	12.8%	0.83 [0.38 , 1.83]
Tarlatzis 2006	3	55	4	59	3.7%	0.80 [0.19 , 3.43]
Subtotal (95% CI)		**667**		**622**	**36.9%**	**0.88 [0.56 , 1.40]**
Total events:	34		36			
Heterogeneity: Tau² = 0.00; Chi² = 1.70, df = 5 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.59)						
10.6.2 Low response						
De Placido 2005	10	65	13	65	14.0%	0.77 [0.36 , 1.63]
Humaidan 2017	31	462	58	477	45.2%	0.55 [0.36 , 0.84]
Musters 2012	3	116	5	128	4.0%	0.66 [0.16 , 2.71]
Subtotal (95% CI)		**643**		**670**	**63.1%**	**0.60 [0.42 , 0.85]**
Total events:	44		76			
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 2.83 (P = 0.005)						
Total (95% CI)		**1310**		**1292**	**100.0%**	**0.69 [0.5 0.92]**
Total events:	78		112			
Heterogeneity: Tau² = 0.00; Chi² = 3.98, df = 8 (P = 0.86); I² = 0%						
Test for overall effect: Z = 2.57 (P = 0.01)						
Test for subgroup differences: Chi² = 1.68, df = 1 (P = 0.19), I² = 40.5%						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 10.7. Comparison 10: Direct comparison: Long GnRH agonist plus rFSH & rLH versu long GnRH agonist plus rFSH, Outcome 7: Ectopic

Study or Subgroup	Long agonist plus rFSH & rLH Events	Total	Lon agonist p SH Events	ts Total	Weight	Risk Ratio M-H, Random, 95% CI
10.7.1 Low response						
Humaidan 2017	0	462	1	477	100.0%	0.34 [0.01 , 8.43]
Subtotal (95% CI)		**462**		**477**	**100.0%**	**0.34 [0.01 , 8.43]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
Total (95% CI)		**462**		**477**	**100.0%**	**0.34 [0.01 , 8.43]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = .51)						
Test for subgroup differen es: Not a plicable						

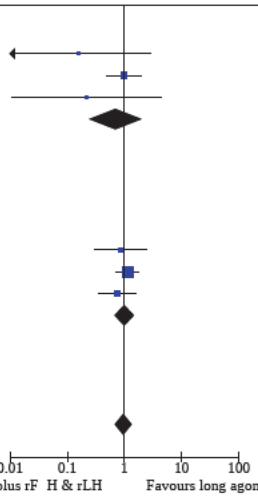


Risk of bias legend
(A) Random seque e generati n (selection bias)
(B) Allocation conceal t lection bias)
(C) Blinding of participants d personnel (performance bias)
(D) Blinding of outcome assessm (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 10.8. Comparison 10: Direct comparison: Long GnRH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH, Outcome 8: Cancellation

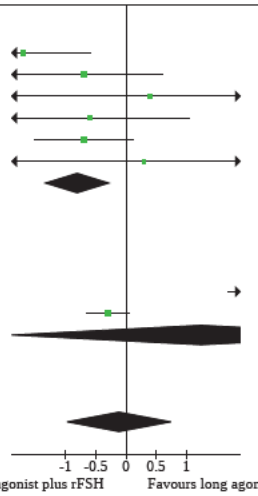
Study or Subgroup	Long agonist plus rFSH & rLH Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
10.8.1 Normal response							
Matorras 2009	0	63	3	68	1.2%	0.15 [0.01 , 2.92]	+ + - - + + +
Nyboe Andersen 2008	15	265	15	261	21.5%	0.98 [0.49 , 1.97]	+ + ? ? + + +
Tarlatzis 2006	0	55	2	59	1.1%	0.21 [0.01 , 4.37]	+ + + + + + +
Subtotal (95% CI)		**383**		**388**	**23.8%**	**0.69 [0.25 , 1.89]**	
Total events:	15		20				
Heterogeneity: Tau² = 0.21; Chi² = 2.34, df = 2 (P = 0.31); I² = 14%							
Test for overall effect: Z = 0.72 (P = 0.47)							
10.8.2 Low response							
De Placido 2005	6	65	7	65	9.7%	0.86 [0.30 , 2.41]	+ + ? + - + +
Humaidan 2017	35	462	32	477	48.6%	1.13 [0.71 , 1.79]	+ + - + + + +
Musters 2012	10	116	15	128	18.0%	0.74 [0.34 , 1.57]	+ + - - - + +
Subtotal (95% CI)		**643**		**670**	**76.2%**	**0.99 [0.68 , 1.43]**	
Total events:	51		54				
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 2 (P = 0.61); I² = 0%							
Test for overall effect: Z = 0.08 (P = 0.94)							
Total (95% CI)		**1026**		**1058**	**100.0%**	**0.95 [0 9 , 1.31]**	
Total events:	66		74				
Heterogeneity: Tau² = 0.00; Chi² = 3.45, df = 5 (P = 0.63); I² = 0%							
Test for overall effect: Z = 0.33 (P = 0.74)							
Test for subgroup differences: Chi² = 0.42, df = 1 (P = 0.51), I² = 0%							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 10.9. Comparison 10: Direct comparison: Long GnRH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH, Outcome 9: Oocyte number

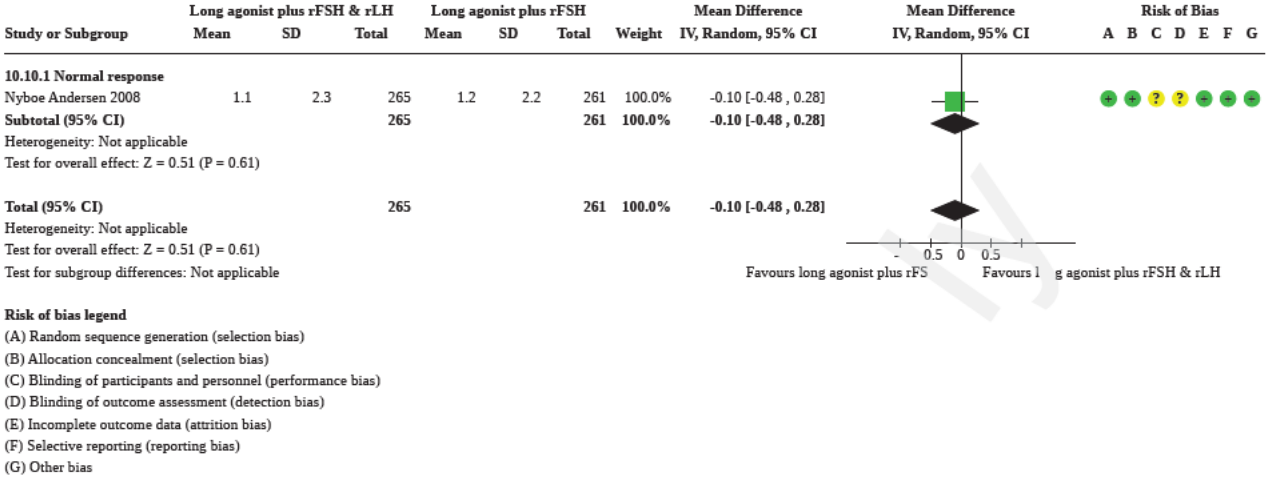
Study or Subgroup	Long agonist plus rFSH & rLH Mean	SD	Total	Long onist p us rFSH Mean	S	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
10.9.1 Normal response									
Fabregues 2011	6.1	3	125	7.8	3.9	62	14.0%	-1.70 [-2.80 , -0.60]	+ + + - + + +
Humaidan 2004	9.3	5.4	6	0	4.7	115	12.8%	-0.70 [-2.01 , 0.61]	+ + + + + + +
Lahoud 2017	12	6.3	4	11.6	5.6	57	7.6%	0.40 [-1.98 , 2.78]	+ + + + + + +
Matorras 2009	8.3	4	6	8.9	4.9	68	10.9%	-0.60 [-2.24 , 1.04]	+ + - - + + +
Nyboe Andersen 2008	8.8	4.	5	9.5	4.8	261	15.6%	-0.70 [-1.52 , 0.12]	+ + ? ? + + +
Tarlatzis 2006	10.1	5.4	55	9.8	7	59	8.0%	0.30 [-1.99 , 2.59]	+ + + + + + +
Subtotal (95% CI)			7			**622**	**69.0%**	**-0.81 [-1.33 , -0.28]**	
Heterogeneity: Tau² = 0.00; Chi² = 4.55, df = 5 (P = 0.47); I² = 0%									
Test for overall effect: Z = 3.02 (P = 0.002)									
10.9.2 Low response									
De Placido 2005	9	4.3	65	6.1	2.6	65	13.3%	2.90 [1.68 , 4.12]	+ + ? + - + +
Humaidan 2017	3	71	462	3.6	2.82	477	17.7%	-0.30 [-0.65 , 0.05]	+ + - + + + +
Subtotal (95% CI)			527			**542**	**31.0%**	**1.24 [-1.89 , 4.38]**	
Heterogeneity: Tau² = 4.9 Chi² = 24 2 df = 1 (P 0.00001); I² = 96%									
Test for overall effect: = 0.78 (P = 0.44)									
Total (95% CI)			**1194**			**1164**	**100.0%**	**-0.12 [-0.98 , 0.74]**	
Heterogeneity: Tau² = 1.06 hi² = 34.51, df = 7 (P < 0.0001); I² = 80%									
Test for overall effect: Z = 0.26 = 0.79)									
Test for subgroup differences: Chi² 1.60, df = 1 (P = 0.21), I² = 37.7%									



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 10.10. Comparison 10: Direct comparison: Long GnRH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH, Outcome 10: Frozen embryo number

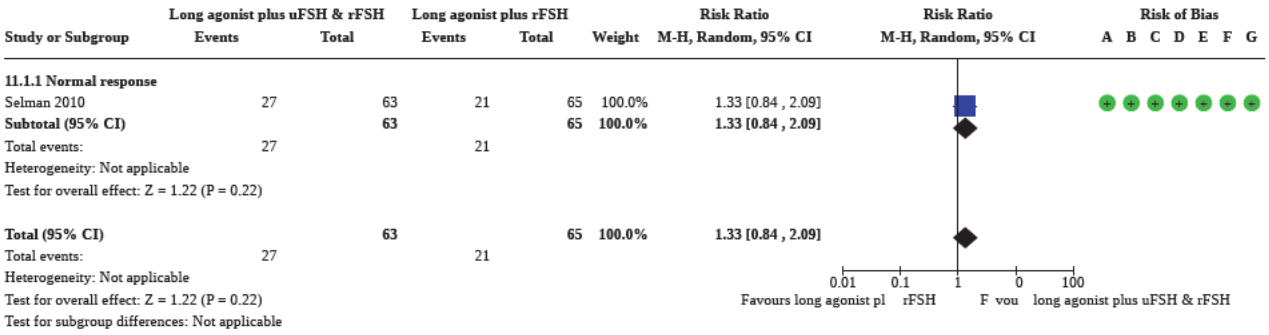


Comparison 11. Direct comparison: Long GnRH agonist plus uFSH & rFSH versus long GnRH agonist plus rFSH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Clinical pregnancy	1	128	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.84, 2.09]
11.1.1 Normal response	1	128	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.84, 2.09]
11.2 Miscarriage	1	128	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.32, 5.90]
11.2.1 Normal response	1	28	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.32, 5.90]
11.3 Cancellation	1	128	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.05, 5.55]
11.3.1 Normal response	1	128	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.05, 5.55]
11.4 Oocyte number	1	128	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.40, 0.20]
11.4.1 Normal response	1	128	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.40, 0.20]

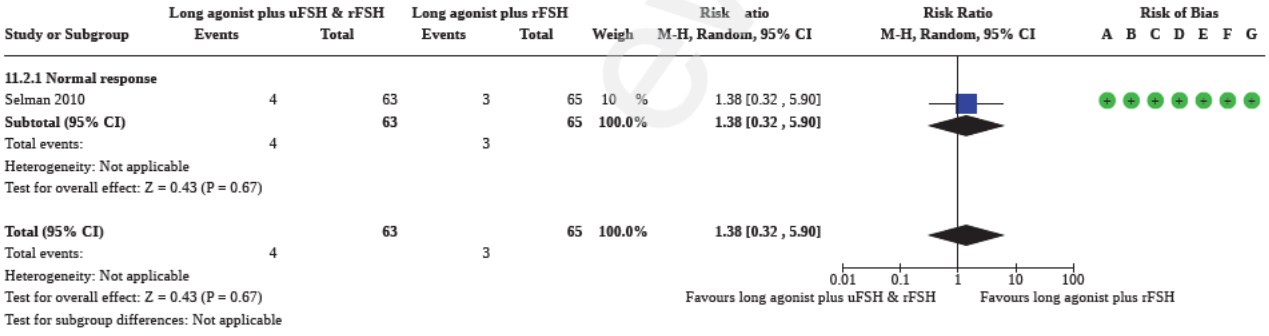
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Analysis 11.1. Comparison 11: Direct comparison: Long GnRH agonist plus uFSH & rFSH versus long GnRH agonist plus rFSH, Outcome 1: Clinical pregnancy



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

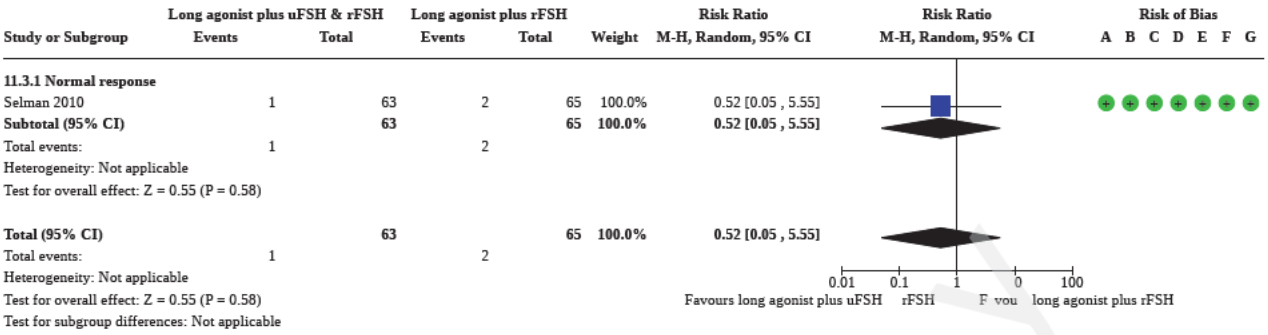
Analysis 11.2. Comparison 11: Direct compar son: Long GnRH agonist plus uFSH & rFSH versus long GnRH agonist pl s rFSH Outcome 2: Miscarriage



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performan bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

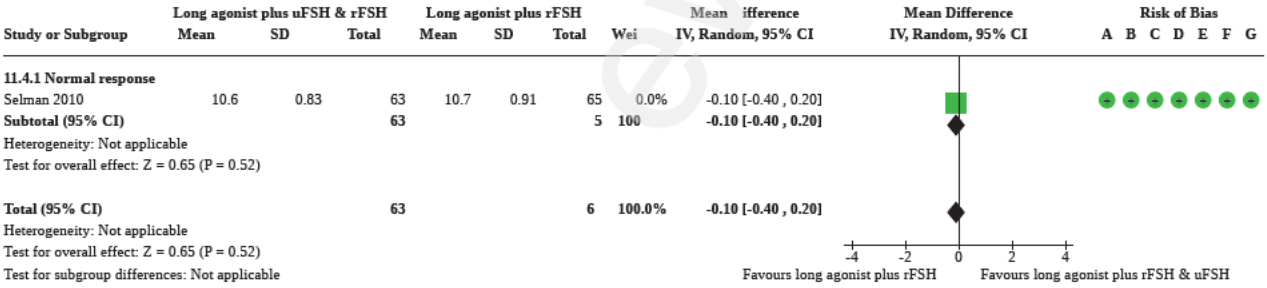
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Analysis 11.3. Comparison 11: Direct comparison: Long GnRH agonist plus uFSH & rFSH versus long GnRH agonist plus rFSH, Outcome 3: Cancellation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 11.4. Comparison 11: Direct comparison: Long GnRH agonist plus uFSH & rFSH versus long GnRH agonist plus rFSH, Outcome 4: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performan bias)
(D) Blinding of outcome assessment (detection bias
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

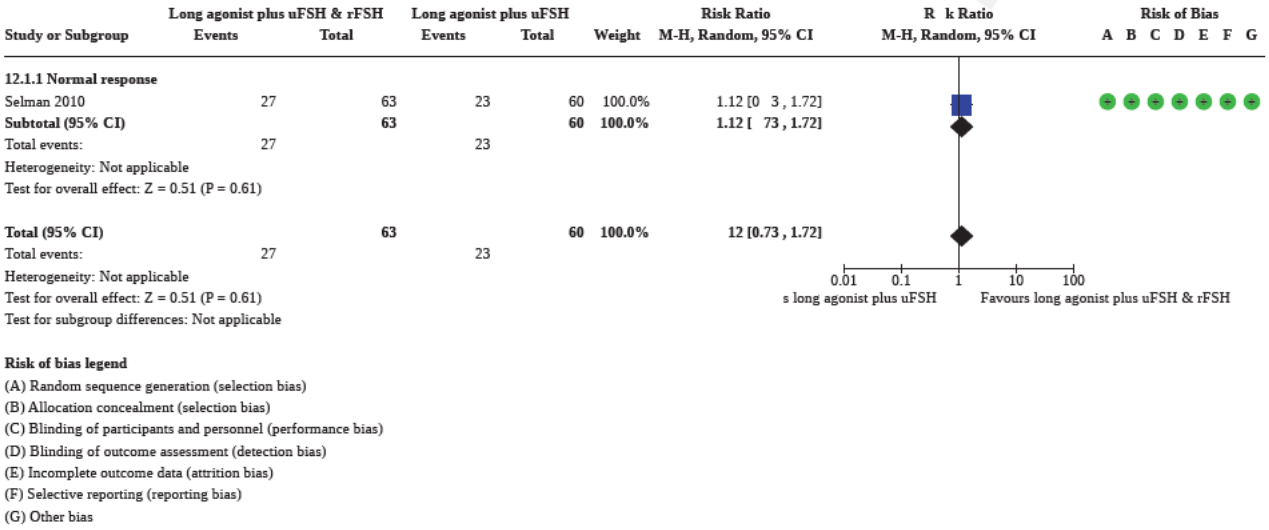
Comparison 12. Direct co aris n: Long GnRH agonist plus uFSH & rFSH versus long GnRH agonist plus uFSH

Outcome or subgr up title	No. o studies	No. of partici-pants	Statistical method	Effect size
12.1 Clinical pregnan y	1	123	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.73, 1.72]
12.1.1 Normal response	1	123	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.73, 1.72]
12.2 Miscarriage	1	123	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.30, 5.44]
12.2.1 Normal response	1	123	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.30, 5.44]
12.3 Cancellation	1	123	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.06, 14.89]

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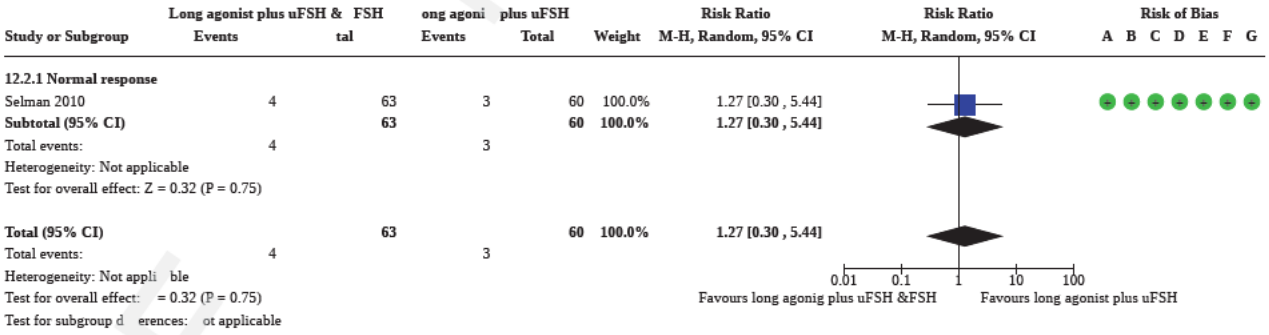
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.3.1 Normal response	1	123	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.06, 14.89]
12.4 Oocyte number	1	123	Mean Difference (IV, Random, 95% CI)	0.00 [-0.29, 0.29]
12.4.1 Normal response	1	123	Mean Difference (IV, Random, 95% CI)	0.00 [-0.29, 0.29]

Analysis 12.1. Comparison 12: Direct comparison: Long GnRH agonis plus uFSH & rFSH versus long GnRH agonist plus uFSH, Outcome 1: Clinical pregnancy



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

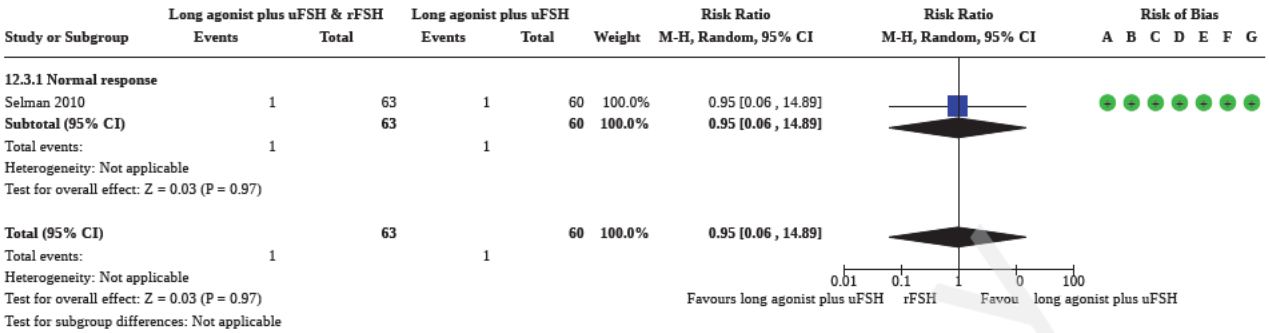
Analysis 12.2. Compar n 12 Direct comparison: Long GnRH agonist plus uFSH & rFSH versus ong GnRH agonist plus uFSH, Outcome 2: Miscarriage



Risk of bias legend
(A) Random sequence generatio election bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

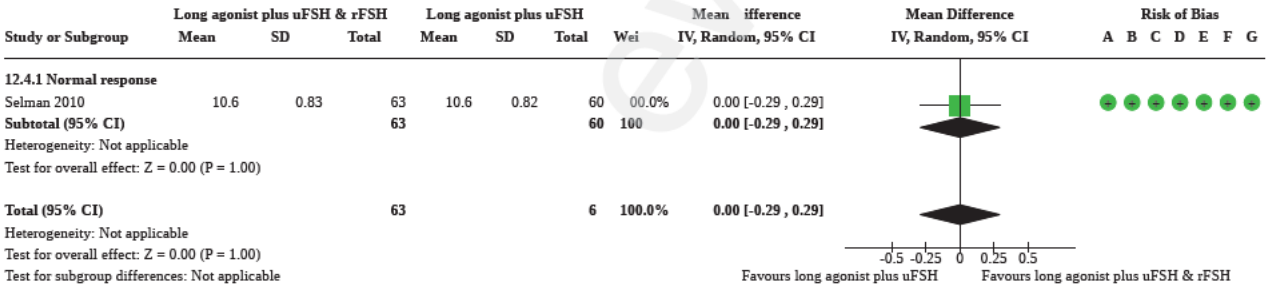
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Analysis 12.3. Comparison 12: Direct comparison: Long GnRH agonist plus uFSH & rFSH versus long GnRH agonist plus uFSH, Outcome 3: Cancellation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 12.4. Comparison 12: Direct compar son: Long GnRH agonist plus uFSH & rFSH versus long GnRH agonist plus uFSH, Outcome 4: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performanc bias)
(D) Blinding of outcome assessment (detection bias
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

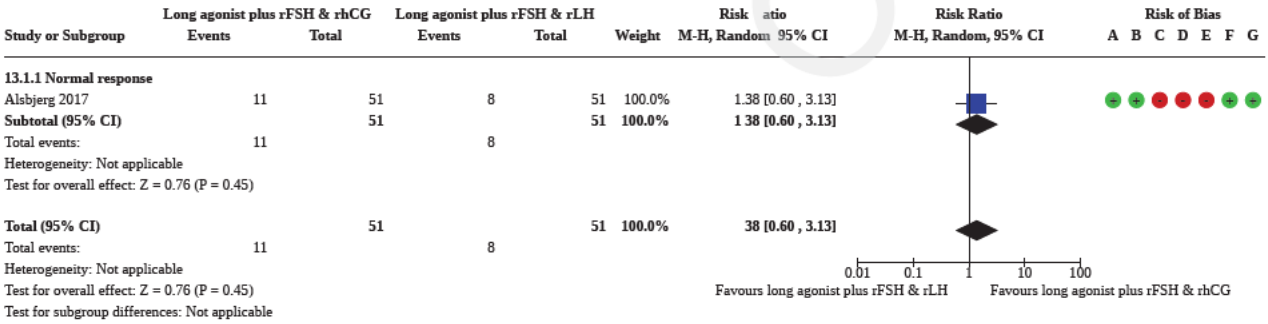
Comparison 13. Direct comparis n: Long GnRH agonist plus rFSH & rhCG versus long GnRH agonist plus rFSH & rLH

Outcome or subgr up title	No. of tudies	No. of partici-pants	Statistical method	Effect size
13.1 Live birth	1	102	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.60, 3.13]
13.1.1 Normal response	1	102	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.60, 3.13]
13.2 OHSS	1	102	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.07]
13.2.1 Normal response	1	102	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.07]
13.3 Clinical pregnancy	1	102	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.59, 2.39]

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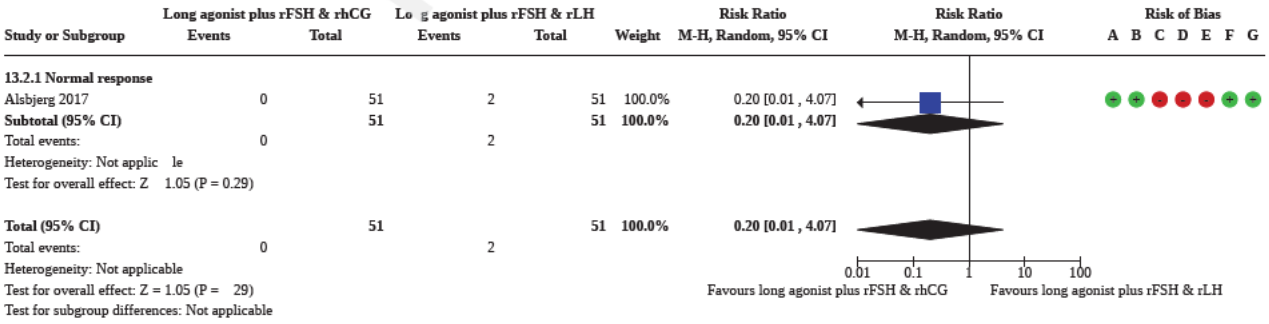
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.3.1 Normal response	1	102	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.59, 2.39]
13.4 Cancellation	1	102	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.47, 2.68]
13.4.1 Normal response	1	102	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.47, 2.68]
13.5 Oocyte number	1	102	Mean Difference (IV, Random, 95% CI)	-0.80 [-2.55, 0.95]
13.5.1 Normal response	1	102	Mean Difference (IV, Random 95% C)	-0.80 [-2.55, 0.95]

Analysis 13.1. Comparison 13: Direct comparison: Long G RH agonist plus rFSH & rhCG versus long GnRH agonist plus rFSH & LH, O tcom 1: Live birth



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 13 2. Comparison 13: Direct comparison: Long GnRH agonist plus rFSH & rhCG ve sus long GnRH agonist plus rFSH & rLH, Outcome 2: OHSS

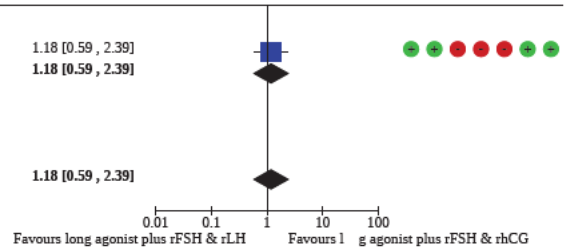


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 13.3. Comparison 13: Direct comparison: Long GnRH agonist plus rFSH & rhCG versus long GnRH agonist plus rFSH & rLH, Outcome 3: Clinical pregnancy

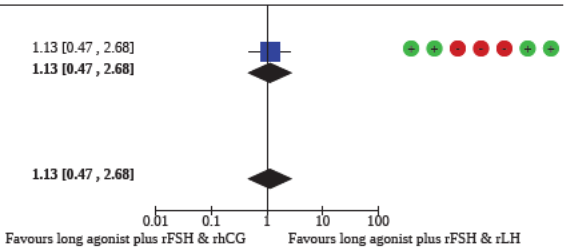
Study or Subgroup	Long agonist plus rFSH & rhCG Events	Total	Long agonist plus rFSH & rLH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
13.3.1 Normal response						
Alsbjerg 2017	13	51	11	51	100.0%	1.18 [0.59 , 2.39]
Subtotal (95% CI)		**51**		**51**	**100.0%**	**1.18 [0.59 , 2.39]**
Total events:	13		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**51**		**51**	**100.0%**	**1.18 [0.59 , 2.39]**
Total events:	13		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 13.4. Comparison 13: Direct compariso : ong GnRH agonist plus rFSH & rhCG versus long GnRH agonist plus rFSH & rLH, Outcome 4: Cancellation

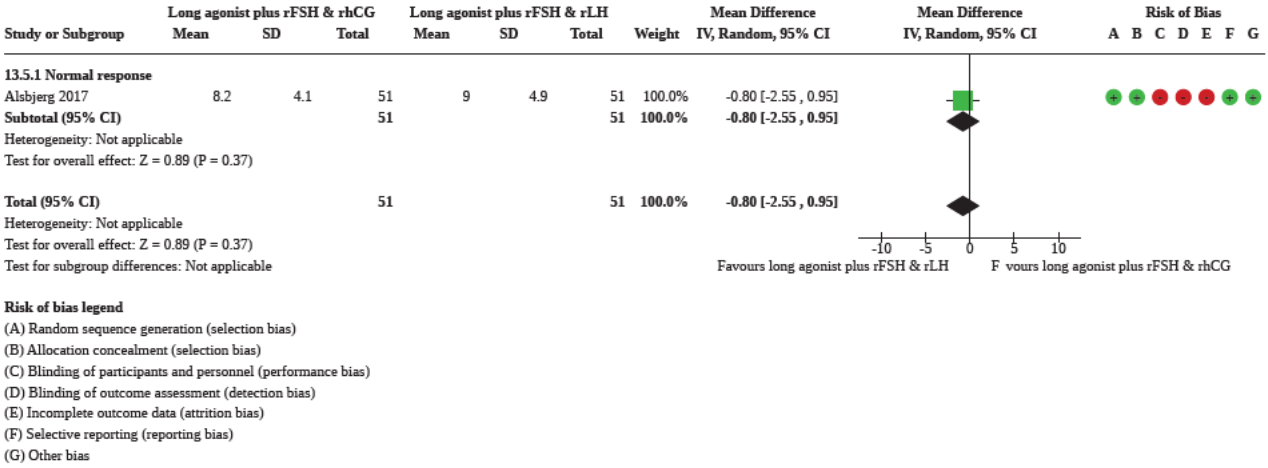
Study or Subgroup	Long agonist plus rFSH & rhCG Events	Total	Long agonist plus rFSH & rLH Events	Total	Weigh	Risk Ratio M H, Random, 95% CI
13.4.1 Normal response						
Alsbjerg 2017	9	51	8	5	100.0%	1.13 [0.47 , 2.68]
Subtotal (95% CI)		**51**		**51**	**1 0%**	**1.13 [0.47 , 2.68]**
Total events:	9		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		**51**		**51**	**100.0%**	**1.13 [0.47 , 2.68]**
Total events:	9		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 13.5. Comparison 13: Direct comparison: Long GnRH agonist plus rFSH & rhCG versus long GnRH agonist plus rFSH & rLH, Outcome 5: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

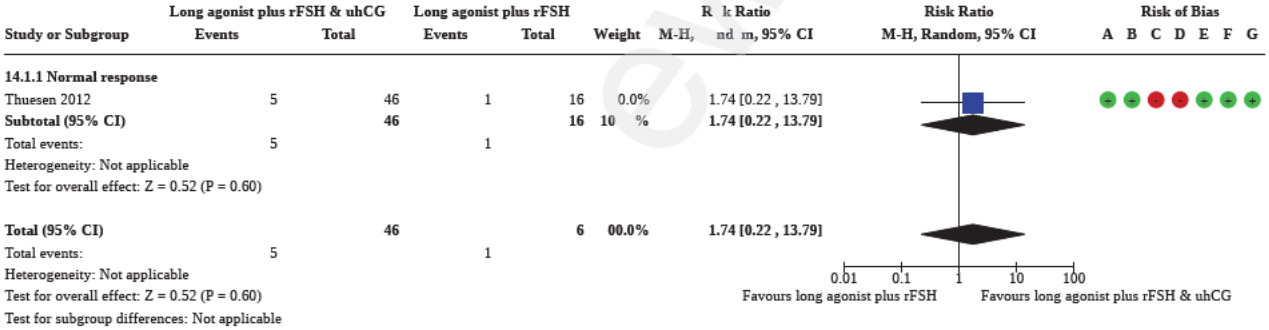
Comparison 14. Direct comparison: Long GnRH agonist plus rFSH & uhCG ersus long GnRH agonist plus rFSH

Outcome or subgroup title	No. of studies	No. of partici-pants	Statist cal method	Effect size
14.1 Live birth	1	62	Risk Ra io (M-H, Random, 95% CI)	1.74 [0.22, 13.79]
14.1.1 Normal response	1	62	Ris Ratio (M-H, Random, 95% CI)	1.74 [0.22, 13.79]
14.2 OHSS	1	62	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.02, 5.24]
14.2.1 Normal response	1	62	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.02, 5.24]
14.3 Clinical pregnancy	2	152	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.64, 1.51]
14.3.1 Normal response	1	62	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.47, 3.16]
14.3.2 High response	1	90	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.57, 1.50]
14.4 Multiple pregnancy	1	90	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.09, 1.57]
14.4.1 High response	1	90	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.09, 1.57]
14.5 Miscarriage	1	62	Risk Ratio (M-H, Random, 95% CI)	2.53 [0.14, 46.52]
14.5.1 Normal response	1	62	Risk Ratio (M-H, Random, 95% CI)	2.53 [0.14, 46.52]
14.6 Ectopic	1	62	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.09, 35.79]
14.6.1 Normal response	1	62	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.09, 35.79]
14.7 Cancellation	1	62	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.05, 25.38]
14.7.1 Normal response	1	62	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.05, 25.38]
14.8 Oocyte number	2	152	Mean Difference (IV, Random, 95% CI)	-1.35 [-3.09, 0.40]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.8.1 Normal response	1	62	Mean Difference (IV, Random, 95% CI)	0.40 [-2.98, 3.78]
14.8.2 High response	1	90	Mean Difference (IV, Random, 95% CI)	-1.80 [-2.52, -1.08]
14.9 Cleavage embryo number	1	62	Mean Difference (IV, Random, 95% CI)	-0.50 [-3.14, 2.14]
14.9.1 Normal response	1	62	Mean Difference (IV, Random, 95% CI)	-0.50 [-3.14, 2.14]
14.10 Frozen embryo number	2	152	Mean Difference (IV, Random, 95% C	-1.21 [-2.68, 0.25]
14.10.1 Normal response	1	62	Mean Difference (IV Random, 95% CI)	-0.10 [-2.09, 1.89]
14.10.2 High response	1	90	Mean Diffe ence (IV, Random, 95% CI)	-1.72 [-2.11, -1.32]

Analysis 14.1. Comparison 14: Direct compa ison: Long GnRH agonist plus rFSH & uhCG versus long GnRH agonist plus rFSH, Outcome 1: Live birth

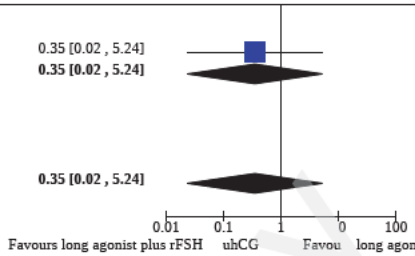


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (perform nce bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 14.2. Comparison 14: Direct comparison: Long GnRH agonist plus rFSH & uhCG versus long GnRH agonist plus rFSH, Outcome 2: OHSS

Study or Subgroup	Long agonist plus rFSH & uhCG Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.2.1 Normal response						
Thuesen 2012	1	46	1	16	100.0%	0.35 [0.02 , 5.24]
Subtotal (95% CI)		**46**		**16**	**100.0%**	**0.35 [0.02 , 5.24]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
Total (95% CI)		**46**		**16**	**100.0%**	**0.35 [0.02 , 5.24]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: Not applicable						

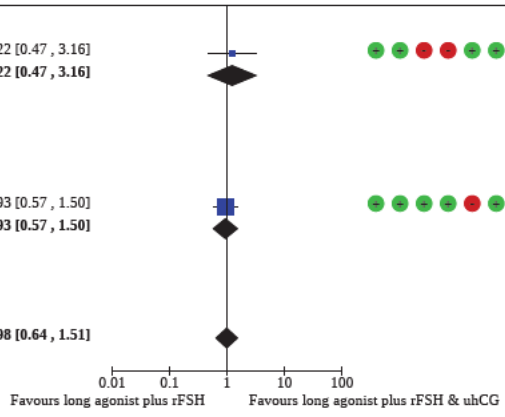




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 14.3. Comparison 14: Direct compariso : Long GnRH agonist plus rFSH & uhCG versus long GnRH agonist plus rFS , Out ome 3: Clinical pregnancy

Study or Subgroup	Long agonist plus rFSH & uhCG Events	Total	Long agonist plus rFSH Events	Total	Weigh	Risk atio M-H, Random, 95% CI
14.3.1 Normal response						
Thuesen 2012	14	46	4	16	2 %	1.22 [0.47 , 3.16]
Subtotal (95% CI)		**46**		**1**	**20.2%**	**1.22 [0.47 , 3.16]**
Total events:	14		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
14.3.2 High response						
Ashrafi 2011	26	60	4	30	79.8%	0.93 [0.57 , 1.50]
Subtotal (95% CI)		**60**		**30**	**79.8%**	**0.93 [0.57 , 1.50]**
Total events:	26		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
Total (95% CI)		**106**		**46**	**100.0%**	**0.98 [0.64 , 1.51]**
Total events:	40		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0); I² = %						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I 0%						

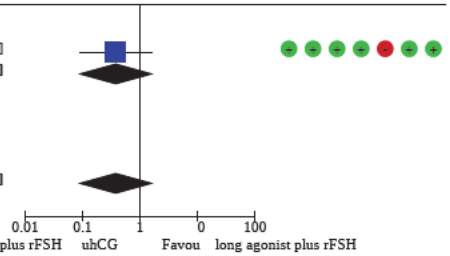


Risk of bias legend
(A) Random sequence generation (selection b
(B) Allocation concealment (selection bias)
(C) Blinding of participants and person (ormanc ias)
(D) Blinding of outcome assessment detection b)
(E) Incomplete outcome data (attriti bias)
(F) Selective reporting (porting bias)
(G) Other bias

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Analysis 14.4. Comparison 14: Direct comparison: Long GnRH agonist plus rFSH & uhCG versus long GnRH agonist plus rFSH, Outcome 4: Multiple pregnancy

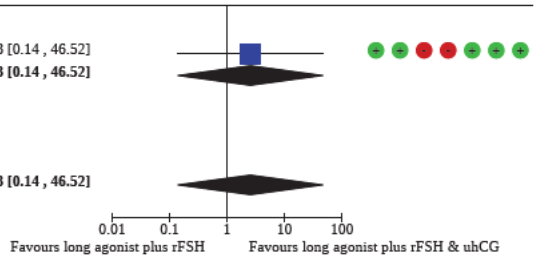
Study or Subgroup	Long agonist plus rFSH & uhCG Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.4.1 High response						
Ashrafi 2011	3	60	4	30	100.0%	0.38 [0.09 , 1.57]
Subtotal (95% CI)		**60**		**30**	**100.0%**	**0.38 [0.09 , 1.57]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						
Total (95% CI)		**60**		**30**	**100.0%**	**0.38 [0.09 , 1.57]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 14.5. Comparison 14: Direct compar son: Long GnRH agonist plus rFSH & uhCG versus long GnRH agonist pl s rFSH Outcome 5: Miscarriage

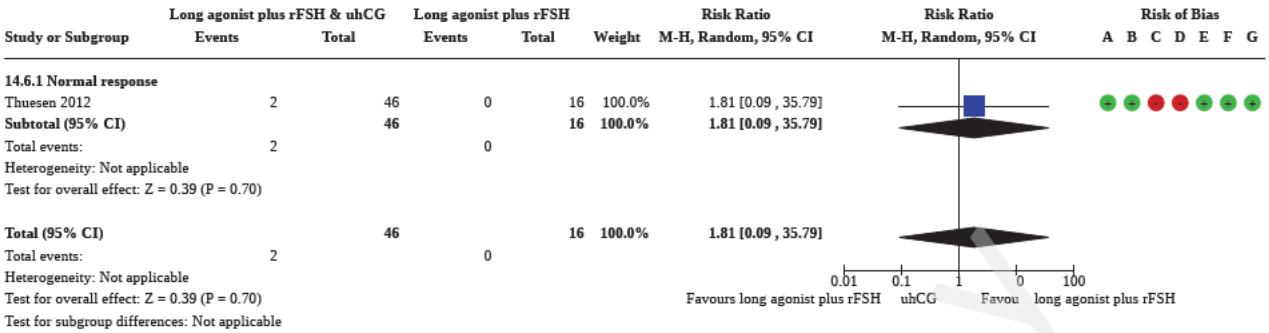
Study or Subgroup	Long agonist plus rFSH & uhCG Events	Total	Long agonist plus rFSH Events	Total	Weigh	Risk atio M-H, Random, 95% CI
14.5.1 Normal response						
Thuesen 2012	3	46	0	16	10 %	2.53 [0.14 , 46.52]
Subtotal (95% CI)		**46**		**1**	**100.0%**	**2.53 [0.14 , 46.52]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**46**		**16**	**100.0%**	**2.53 [0.14 , 46.52]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performan bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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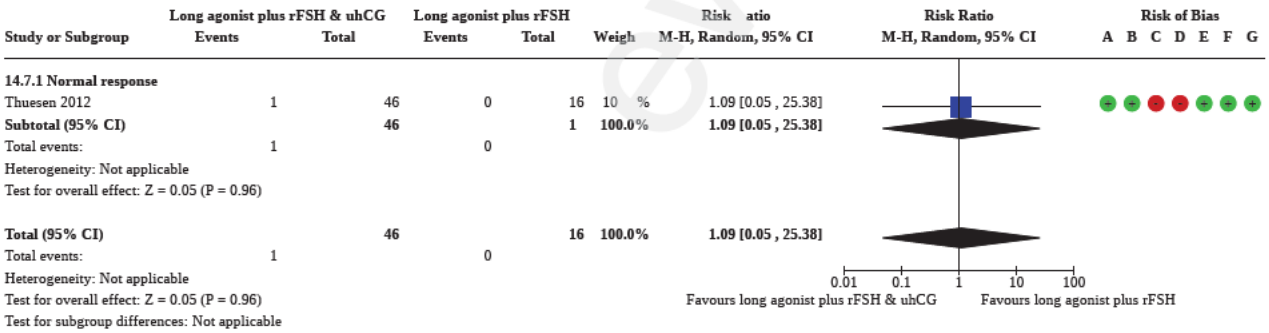
Analysis 14.6. Comparison 14: Direct comparison: Long GnRH agonist plus rFSH & uhCG versus long GnRH agonist plus rFSH, Outcome 6: Ectopic



Study or Subgroup	Long agonist plus rFSH & uhCG Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.6.1 Normal response						
Thuesen 2012	2	46	0	16	100.0%	1.81 [0.09 , 35.79]
Subtotal (95% CI)		**46**		**16**	**100.0%**	**1.81 [0.09 , 35.79]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Total (95% CI)		**46**		**16**	**100.0%**	**1.81 [0.09 , 35.79]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Not applicable						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 14.7. Comparison 14: Direct comparison: Long GnRH agonist plus rFSH & uhCG versus long GnRH agonist plus rFSH, Outcome 7: Cancellation



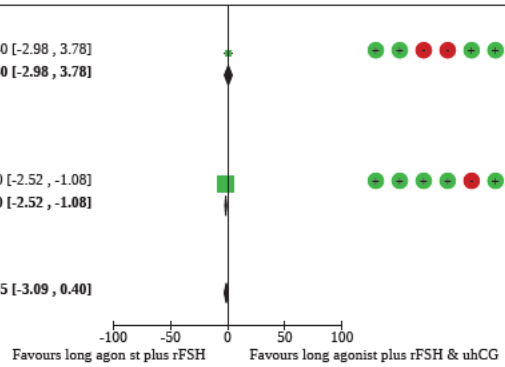
Study or Subgroup	Long agonist plus rFSH & uhCG Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.7.1 Normal response						
Thuesen 2012	1	46	0	16	100.0%	1.09 [0.05 , 25.38]
Subtotal (95% CI)		**46**		**16**	**100.0%**	**1.09 [0.05 , 25.38]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
Total (95% CI)		**46**		**16**	**100.0%**	**1.09 [0.05 , 25.38]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Not applicable						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 14.8. Comparison 14: Direct comparison: Long GnRH agonist plus rFSH & uhCG versus long GnRH agonist plus rFSH, Outcome 8: Oocyte number

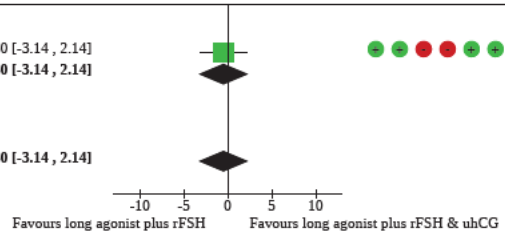
Study or Subgroup	Long agonist plus rFSH & uhCG Mean	SD	Total	Long agonist plus rFSH Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
14.8.1 Normal response								
Thuesen 2012	9.7	4.8	46	9.3	6.3	16	20.6%	0.40 [-2.98 , 3.78]
Subtotal (95% CI)			**46**			**16**	**20.6%**	**0.40 [-2.98 , 3.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.23 (P = 0.82)								
14.8.2 High response								
Ashrafi 2011	11.9	1.59	60	13.7	1.66	30	79.4%	-1.80 [-2.52 , -1.08]
Subtotal (95% CI)			**60**			**30**	**79.4%**	**-1.80 [-2.52 , -1.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.92 (P < 0.00001)								
Total (95% CI)			**106**			**46**	**100.0%**	**-1.35 [-3.09 , 0.40]**
Heterogeneity: Tau² = 0.86; Chi² = 1.55, df = 1 (P = 0.21); I² = 36%								
Test for overall effect: Z = 1.51 (P = 0.13)								
Test for subgroup differences: Chi² = 1.55, df = 1 (P = 0.21), I² = 35.6%								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 14.9. Comparison 14: Direct comparison Long GnRH agonist plus rFSH & uhCG versus long GnRH agonist plus rFSH, Outcome 9: Cleavage embryo number

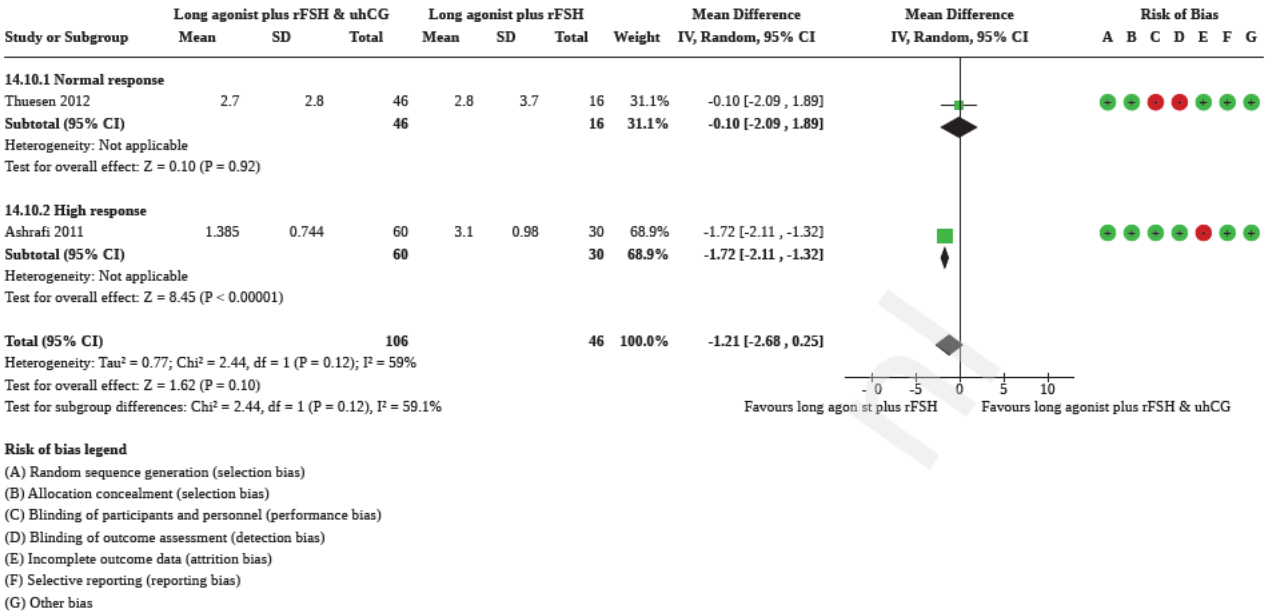
Study or Subgroup	Long agonist plus rFSH & uhCG Mean	SD	Total	Long agonist plus FSH Mean	SD	Tot	Weig	Mean Difference IV, Random, 95% CI
14.9.1 Normal response								
Thuesen 2012	5.9	4.5	46	6.4	4.7	16	100.0%	-0.50 [-3.14 , 2.14]
Subtotal (95% CI)			**46**				**100.0%**	**-0.50 [-3.14 , 2.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								
Total (95% CI)			**46**			**16**	**100.0%**	**-0.50 [-3.14 , 2.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 14.10. Comparison 14: Direct comparison: Long GnRH agonist plus rFSH & uhCG versus long GnRH agonist plus rFSH, Outcome 10: Frozen embryo number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

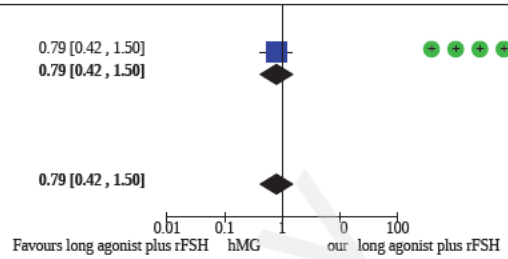
Comparison 15. Direct comparison: Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus rFSH

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
15.1 OHSS	1	695	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.42, 1.50]
15.1.1 Normal response	1	695	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.42, 1.50]
15.2 Clinical pregnancy	1	6 0	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.93, 1.59]
15.2.1 Normal response	1	610	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.93, 1.59]
15.3 Ongoing pregnancy	1	610	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.97, 1.67]
15.3.1 Normal response	1	610	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.97, 1.67]
15.4 Multiple pregnancy	1	610	Risk Ratio (M-H, Random, 95% CI)	2.17 [1.27, 3.70]
15.4.1 Normal response	1	610	Risk Ratio (M-H, Random, 95% CI)	2.17 [1.27, 3.70]
15.5 Cancellation		1305	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.68, 1.29]
15.5.1 Normal resp nse	2	1305	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.68, 1.29]
15.6 Oocyte number	2	1305	Mean Difference (IV, Random, 95% CI)	-0.23 [-1.01, 0.55]
15.6.1 Normal response	2	1305	Mean Difference (IV, Random, 95% CI)	-0.23 [-1.01, 0.55]

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Analysis 15.1. Comparison 15: Direct comparison: Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus rFSH, Outcome 1: OHSS

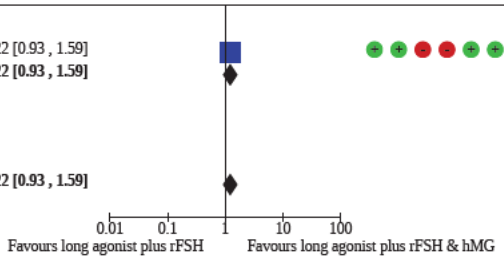
Study or Subgroup	Long agonist plus rFSH & hMG Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
15.1.1 Normal response							
Melo 2010	16	349	20	346	100.0%	0.79 [0.42 , 1.50]	+ + + + - + +
Subtotal (95% CI)		**349**		**346**	**100.0%**	**0.79 [0.42 , 1.50]**	
Total events:	16		20				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.71 (P = 0.48)							
Total (95% CI)		**349**		**346**	**100.0%**	**0.79 [0.42 , 1.50]**	
Total events:	16		20				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.71 (P = 0.48)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 15.2. Comparison 15: Direct compari on: Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus rFSH Outcome 2: Clinical pregnancy

Study or Subgroup	Long agonist plus rFSH & hMG Events	Total	Long agonist plus rFSH Events	Total	Weigh	isk atio M H, Random, 95% CI	Risk of Bias A B C D E F G
15.2.1 Normal response							
Shu 2019	89	305	73	305	10 %	1.22 [0.93 , 1.59]	+ + - - + + -
Subtotal (95% CI)		**305**		**305**	**100.0%**	**1.22 [0.93 , 1.59]**	
Total events:	89		73				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.46 (P = 0.14)							
Total (95% CI)		**305**		**305**	**100.0%**	**1.22 [0.93 , 1.59]**	
Total events:	89		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.46 (P = 0.14)							
Test for subgroup differences: Not applicable							

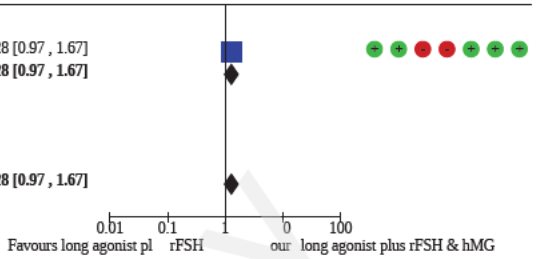


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performan bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 15.3. Comparison 15: Direct comparison: Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus rFSH, Outcome 3: Ongoing pregnancy

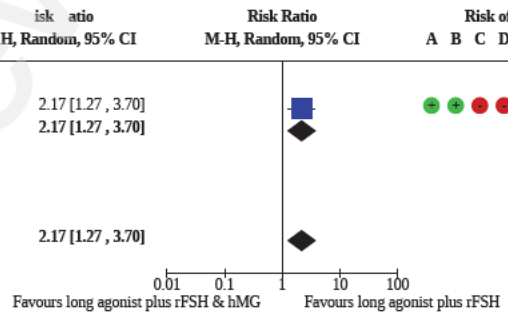
Study or Subgroup	Long agonist plus rFSH & hMG Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
15.3.1 Normal response						
Shu 2019	88	305	69	305	100.0%	1.28 [0.97 , 1.67]
Subtotal (95% CI)		**305**		**305**	**100.0%**	**1.28 [0.97 , 1.67]**
Total events:	88		69			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
Total (95% CI)		**305**		**305**	**100.0%**	**1.28 [0.97 , 1.67]**
Total events:	88		69			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 15.4. Comparison 15: Direct compariso : Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus rFSH Outc me 4: Multiple pregnancy

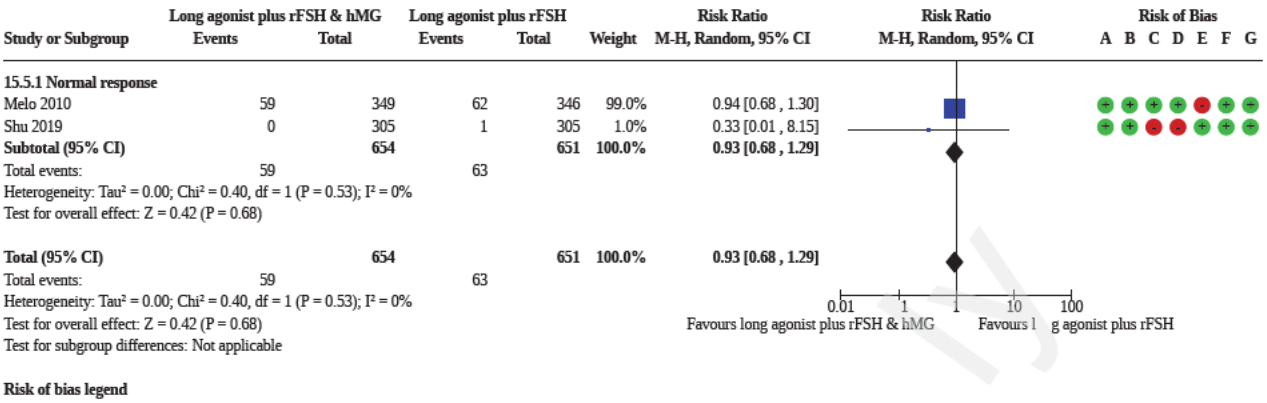
Study or Subgroup	Long agonist plus rFSH & hMG Events	Total	Long agonist plus rFSH Events	Total	Weigh	isk atio M H, Random, 95% CI
15.4.1 Normal response						
Shu 2019	39	305	18	305	10 %	2.17 [1.27 , 3.70]
Subtotal (95% CI)		**305**		**305**	**100.0%**	**2.17 [1.27 , 3.70]**
Total events:	39		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.83 (P = 0.005)						
Total (95% CI)		**305**		**305**	**100.0%**	**2.17 [1.27 , 3.70]**
Total events:	39		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.83 (P = 0.005)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performan bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

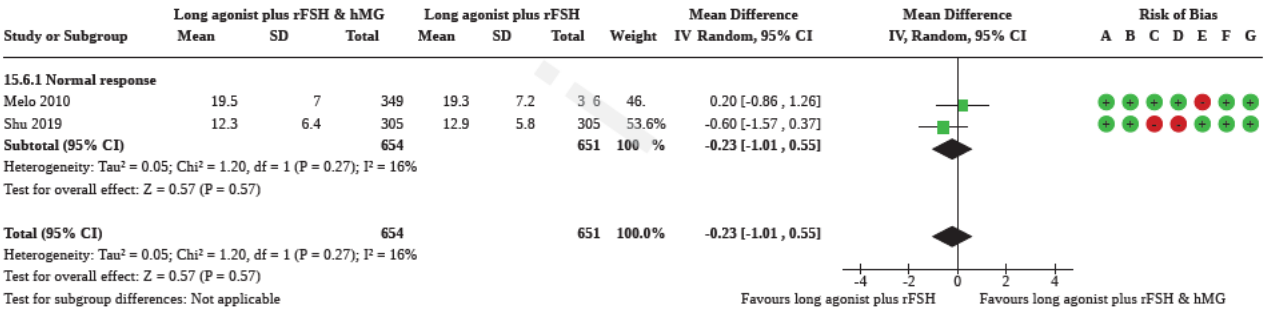
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Analysis 15.5. Comparison 15: Direct comparison: Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus rFSH, Outcome 5: Cancellation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 15.6. Comparison 15: Direct com aris n: Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus rFSH, Outcome 6: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performan bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

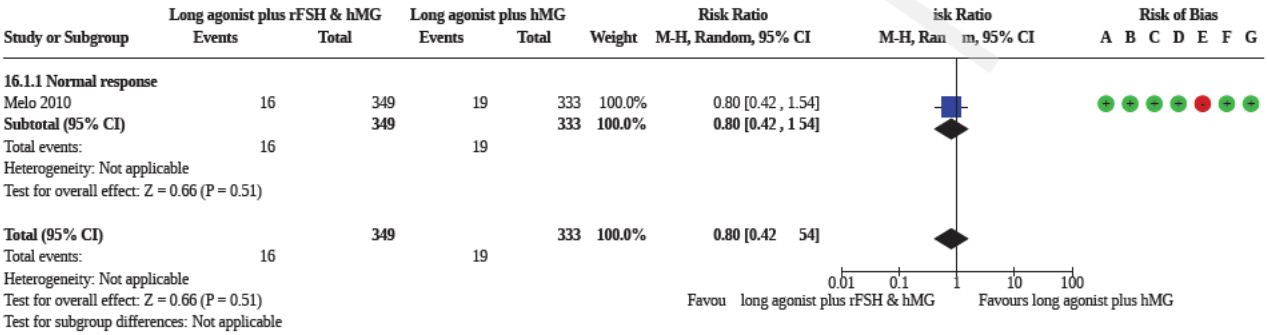
Comparison 16. Direct ompar son: Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus hMG

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
16.1 OHSS	1	682	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.42, 1.54]
16.1.1 Normal response	1	682	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.42, 1.54]
16.2 Cancellation	1	682	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.76, 1.49]
16.2.1 Normal response	1	682	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.76, 1.49]

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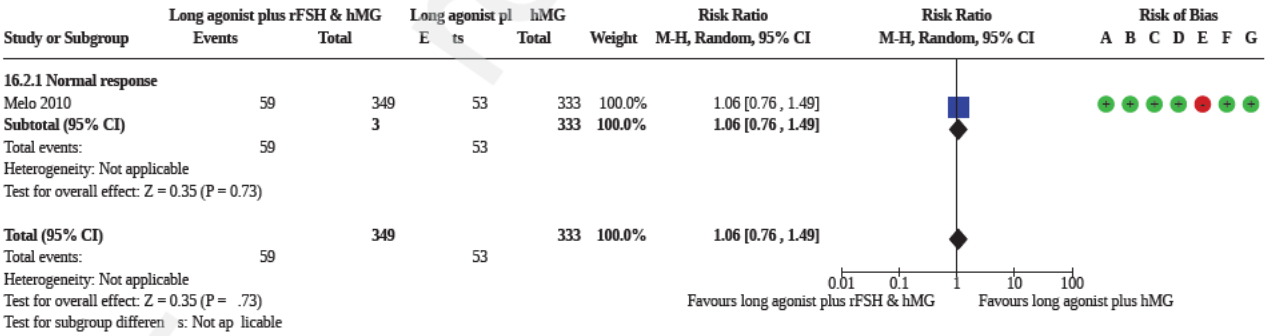
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.3 Oocyte number	1	682	Mean Difference (IV, Random, 95% CI)	0.80 [-0.21, 1.81]
16.3.1 Normal response	1	682	Mean Difference (IV, Random, 95% CI)	0.80 [-0.21, 1.81]

Analysis 16.1. Comparison 16: Direct comparison: Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus hMG, Outcome 1: OHSS



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

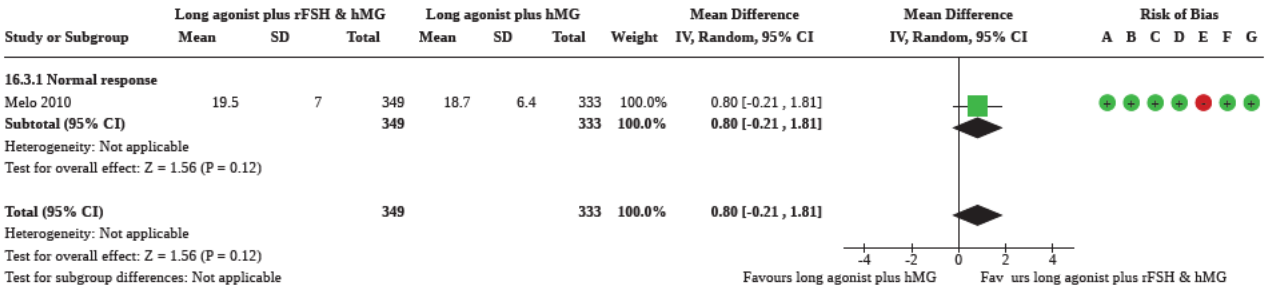
Analysis 16.2. Comparison 16: Direct comparison: Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus hMG, Outcome 2: Cancellation



Risk of bias legend
(A) Random sequen genera n (selection bias)
(B) Allocation concealm election bias)
(C) Blinding of participants a personnel (performance bias)
(D) Blinding of outcome assessme (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 16.3. Comparison 16: Direct comparison: Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus hMG, Outcome 3: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 17. Direct comparison: Short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH

Outcome or subgroup title	No. of studies	No. of participants	Statistic l method	Effect size
17.1 Live birth	3	1648	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.95, 1.27]
17.1.1 Normal response	2	1029	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.89, 1.31]
17.1.2 High response	1	619	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.89, 1.42]
17.2 OHSS	3	1648	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.36, 1.93]
17.2.1 Normal response	2	1029	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.65, 2.48]
17.2.2 High response	1	619	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.30, 0.68]
17.3 Clinical pregnancy	2	1029	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.90, 1.27]
17.3.1 Normal response	2	1029	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.90, 1.27]
17.4 Ongoing pregnancy	3	1648	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.96, 1.28]
17.4.1 Normal response	2	1029	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.89, 1.30]
17.4.2 High respon e	1	619	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.92, 1.45]
17.5 Multiple preg ancy	1	749	Risk Ratio (M-H, Random, 95% CI)	9.02 [0.49, 167.02]
17.5.1 Normal response	1	749	Risk Ratio (M-H, Random, 95% CI)	9.02 [0.49, 167.02]
17.6 Miscarriage	3	1648	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.62, 1.28]
17.6.1 Normal response	2	1029	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.73, 1.58]
17.6.2 High response	1	619	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.35, 1.09]

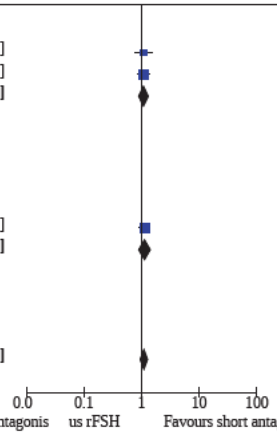
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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.7 Cancellation	3	1648	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.67, 4.46]
17.7.1 Normal response	2	1029	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.67, 1.93]
17.7.2 High response	1	619	Risk Ratio (M-H, Random, 95% CI)	5.98 [1.78, 20.10]
17.8 Oocyte number	3	1648	Mean Difference (IV, Random, 95% CI)	-3.87 [-7.08, -0.67]
17.8.1 Normal response	2	1029	Mean Difference (IV, Random, 95% CI)	-2.16 [-3.59, -0.74]
17.8.2 High response	1	619	Mean Difference (IV, Random, 95% CI)	-7.10 [-8.81, -5.39]
17.9 Cleavage embryo number	1	749	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.28, -0.32]
17.9.2 Normal response	1	749	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.28, -0.32]
17.10 Blastocyst number	2	1367	Mean Difference (IV, Random, 95% CI)	-1.63 [-4.07, 0.82]
17.10.1 Normal response	1	748	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.80, -0.00]
17.10.2 High response	1	619	Mean Difference (IV, Random, 95% CI)	-2.90 [-3.69, -2.11]
17.11 Frozen embryo number	1	280	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.57, 0.37]
17.11.1 Normal response	1	280	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.57, 0.37]

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Analysis 17.1. Comparison 17: Direct comparison: Short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH, Outcome 1: Live birth

Study or Subgroup	Short antagonist plus hMG Events	Total	Short antagonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
17.1.1 Normal response						
Bosch 2008	48	140	44	140	19.4%	1.09 [0.78 , 1.53]
Devroey 2012	105	374	98	375	39.5%	1.07 [0.85 , 1.36]
Subtotal (95% CI)		**514**		**515**	**58.9%**	**1.08 [0.89 , 1.31]**
Total events:	153		142			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.43)						
17.1.2 High response						
Witz 2020	105	310	93	309	41.1%	1.13 [0.89 , 1.42]
Subtotal (95% CI)		**310**		**309**	**41.1%**	**1.13 [0.89 , 1.42]**
Total events:	105		93			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
Total (95% CI)		**824**		**824**	**100.0%**	**1.10 [0.95 , 1.27]**
Total events:	258		235			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 2 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.21)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%						

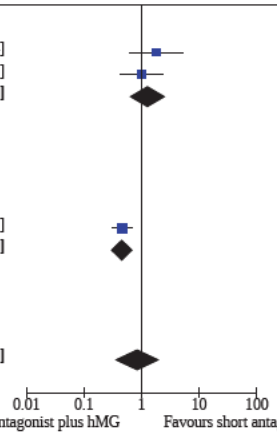




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 17.2. Comparison 17: Dire comparison: Short GnRH antagonist plus hMG versus short GnRH an agonist plus rFSH, Outcome 2: OHSS

Study or Subgroup	Short antagonist plus hMG Events	Total	Short antagonist plus rFSH Events	Tota	W ight	Risk Ratio M-H, Random, 95% CI
17.2.1 Normal response						
Bosch 2008	9	140		40	26.6%	1.80 [0.62 , 5.24]
Devroey 2012	10	374	10	375	31.2%	1.00 [0.42 , 2.38]
Subtotal (95% CI)		**514**		**515**	**57.8%**	**1.26 [0.65 , 2.48]**
Total events:	19		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 1 (P = 0.40 I = %						
Test for overall effect: Z = 0.68 (P = 0.49)						
17.2.2 High response						
Witz 2020	30	310	66	309	42.2%	0.45 [0.30 , 0.68]
Subtotal (95% CI)		**310**		**309**	**42.2%**	**0.45 [0.30 , 0.68]**
Total events:	30		66			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.86 (P = 0.0001)						
Total (95% CI)		**24**		**824**	**100.0%**	**0.84 [0.36 , 1.93]**
Total events:	49		81			
Heterogeneity: Tau² = 0.39 Chi² = 7 0, df = 2 (P 0.03); I² = 73%						
Test for overall effect: Z 0.42 (P = 0.						
Test for subgroup diff ences: Ch ² = 6.60, df = 1 (P = 0.01), I² = 84.8%						



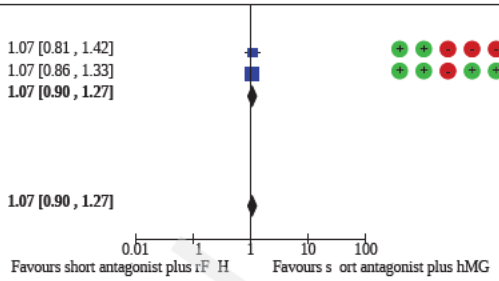


Risk of bias legend
(A) Random sequence gener n (selection bias)
(B) Allocation concealment (selec bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 17.3. Comparison 17: Direct comparison: Short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH, Outcome 3: Clinical pregnancy

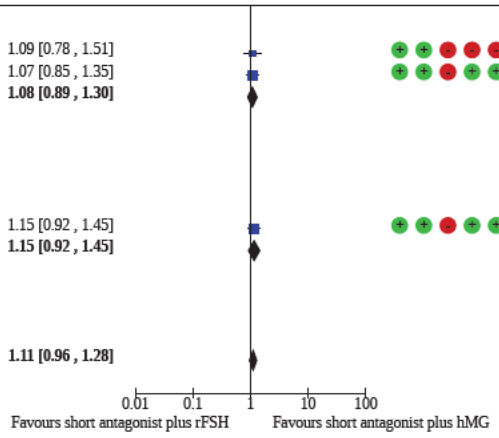
Study or Subgroup	Short antagonist plus hMG Events	Total	Short antagonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
17.3.1 Normal response								
Bosch 2008	59	140	55	140	37.4%	1.07 [0.81 , 1.42]		
Devroey 2012	116	374	109	375	62.6%	1.07 [0.86 , 1.33]		
Subtotal (95% CI)		**514**		**515**	**100.0%**	**1.07 [0.90 , 1.27]**		
Total events:	175		164					
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 0.76 (P = 0.45)								
Total (95% CI)		**514**		**515**	**100.0%**	**1.07 [0.90 , 1.27]**		
Total events:	175		164					
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 0.76 (P = 0.45)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 17.4. Comparison 17: Direct comparison Short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH, Outcome 4: Ongoing pregnancy

Study or Subgroup	Short antagonist plus hMG Events	Total	Short antagonist plus rFSH Events	Total	We ght	Risk Ratio -H Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
17.4.1 Normal response								
Bosch 2008	49	140	45	140	19.2%	1.09 [0.78 , 1.51]		
Devroey 2012	108	374	101	75	3 %	1.07 [0.85 , 1.35]		
Subtotal (95% CI)		**514**		**5**	**58.6%**	**1.08 [0.89 , 1.30]**		
Total events:	157		146					
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%								
Test for overall effect: Z = 0.78 (P = 0.44)								
17.4.2 High response								
Witz 2020	110	310	95	309	41.4%	1.15 [0.92 , 1.45]		
Subtotal (95% CI)		**310**		**309**	**41.4%**	**1.15 [0.92 , 1.45]**		
Total events:	110		95					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.25 (P = 0.21)								
Total (95% CI)		**24**		**824**	**100.0%**	**1.11 [0.96 , 1.28]**		
Total events:	267		241					
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 2 (P = 0.90); I² = 0								
Test for overall effect: Z = 1.40 (P = 0.16)								
Test for subgroup differences: Chi² = 0.21, df = (P = 0.65), I² = 0%								

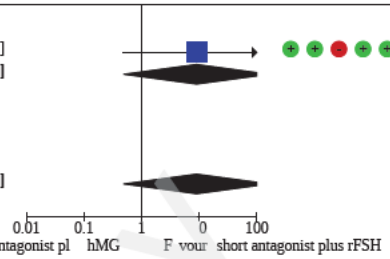


Risk of bias legend
(A) Random sequence generation (sele on)
(B) Allocation concealment (selectio bias)
(C) Blinding of participan and pers nnel (performance bias)
(D) Blinding of outcom ssessment (d ction b s)
(E) Incomplete outco data (att ion bias)
(F) Selective repor g (reporti g bias)
(G) Other bias

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Analysis 17.5. Comparison 17: Direct comparison: Short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH, Outcome 5: Multiple pregnancy

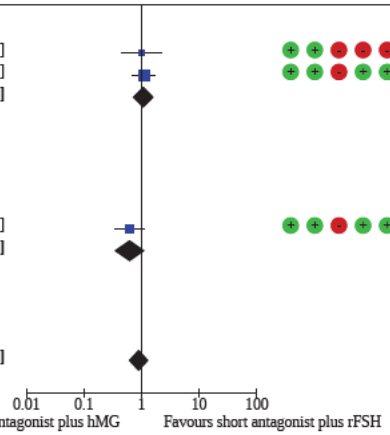
Study or Subgroup	Short antagonist plus hMG Events	Total	Short antagonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
17.5.1 Normal response							
Devroey 2012	4	374	0	375	100.0%	9.02 [0.49 , 167.02]	+ + - + + + -
Subtotal (95% CI)		**374**		**375**	**100.0%**	**9.02 [0.49 , 167.02]**	
Total events:	4		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.48 (P = 0.14)							
Total (95% CI)		**374**		**375**	**100.0%**	**9.02 [0.49 , 167.02]**	
Total events:	4		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.48 (P = 0.14)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 17.6. Comparison 17: Direct compar son: Short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH, Outcome 6: Miscarriage

Study or Subgroup	Short antagonist plus hMG Events	Total	Short antagonist plus rFSH Events	Total	Weigh	Risk atio M H, Random, 95% CI	Risk of Bias A B C D E F G
17.6.1 Normal response							
Bosch 2008	11	140	11	140	1 %	1.00 [0.45 , 2.23]	+ + - - - + -
Devroey 1995	37	374	34	375	48.3%	1.09 [0.70 , 1.70]	+ + - + + + -
Subtotal (95% CI)		**514**		**15**	6 7%	**1.07 [0.73 , 1.58]**	
Total events:	48		45				
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.85); I² = 0%							
Test for overall effect: Z = 0.34 (P = 0.74)							
17.6.2 High response							
Witz 2020	18	310	2	09	33.3%	0.62 [0.35 , 1.09]	+ + - + + + -
Subtotal (95% CI)		**310**		**309**	**33.3%**	**0.62 [0.35 , 1.09]**	
Total events:	18		29				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.66 (P = 0.10)							
Total (95% CI)		**824**		**824**	**100.0%**	**0.89 [0.62 , 1.28]**	
Total events:	66		74				
Heterogeneity: Tau² = 0.02; Chi² = 2.47, df = 2 (P = 0.29); 19%							
Test for overall effect: Z = 0.63 (P = 0.53)							
Test for subgroup differences: Chi² = 2.44, df = 1 (P = 0.12), I² = 59.0%							

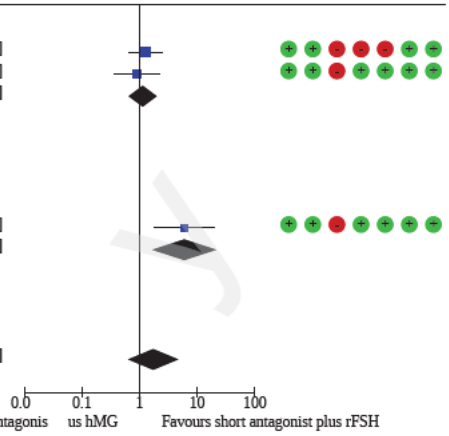


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection b s)
(C) Blinding of participants and pers nnel (perfo ance bias)
(D) Blinding of outcome a essment detection bia)
(E) Incomplete outcome ata (attrition s)
(F) Selective reportin (reporting ias)
(G) Other bias

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Analysis 17.7. Comparison 17: Direct comparison: Short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH, Outcome 7: Cancellation

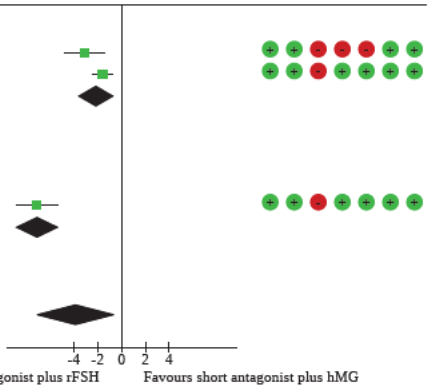
Study or Subgroup	Short antagonist plus hMG Events	Total	Short antagonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
17.7.1 Normal response						
Bosch 2008	18	140	14	140	39.1%	1.29 [0.67 , 2.48]
Devroey 2012	9	374	10	375	33.9%	0.90 [0.37 , 2.20]
Subtotal (95% CI)		**514**		**515**	**73.0%**	**1.13 [0.67 , 1.93]**
Total events:	27		24			
Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
17.7.2 High response						
Witz 2020	18	310	3	309	27.0%	5.98 [1.78 , 20.10]
Subtotal (95% CI)		**310**		**309**	**27.0%**	**5.98 [1.78 , 20.10]**
Total events:	18		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.89 (P = 0.004)						
Total (95% CI)		**824**		**824**	**100.0%**	**1.73 [0.67 , 4.46]**
Total events:	45		27			
Heterogeneity: Tau² = 0.49; Chi² = 6.70, df = 2 (P = 0.04); I² = 70%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Chi² = 6.07, df = 1 (P = 0.01), I² = 83.5%						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 17.8. Comparison 17: Dire comparison: Short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH, Outcome 8: Oocyte number

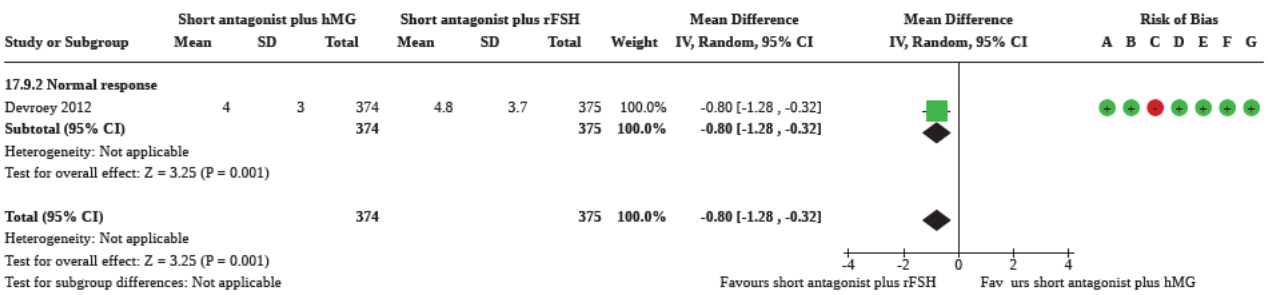
Study or Subgroup	Short antagonist plus hMG Mean	SD	Total	Short antagonist plus rFSH Mean	SD	1	Weight	Mean Difference IV, Random, 95% CI
17.8.1 Normal response								
Bosch 2008	11.3	6	140	14.4	1	140	32.6%	-3.10 [-4.77 , -1.43]
Devroey 2012	9.1	5.2	374	10 7	5.8	375	35.0%	-1.60 [-2.39 , -0.81]
Subtotal (95% CI)			**514**			**515**	**67.6%**	**-2.16 [-3.59 , -0.74]**
Heterogeneity: Tau² = 0.68; Chi² = 2.53, df = 1 (P = 0.11); I² = 61%								
Test for overall effect: Z = 2.98 (P = 0.003)								
17.8.2 High response								
Witz 2020	15.1	10.12	310	22.2	11.54	309	32.4%	-7.10 [-8.81 , -5.39]
Subtotal (95% CI)			**3**			**309**	**32.4%**	**-7.10 [-8.81 , -5.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.14 (P < 0.00001)								
Total (95% CI)			**824**			**824**	**100.0%**	**-3.87 [-7.08 , -0.67]**
Heterogeneity: Tau² = 7.48; Chi² = 33.09, df = 2 (P 0.00001); I² = 94%								
Test for overall effect: Z = 2.37 (P = 0 0)								
Test for subgroup differences: Chi² = 8.92, df = (P < 0.0001), I² = 94.7%								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation conc lment (se tion bias)
(C) Blinding of particip s d personnel (performance bias)
(D) Blinding of outcome ass ment (detection bias)
(E) Incomplete outcome data (att on bias)
(F) Selective reporting (reporting bias)
(G) Other bias

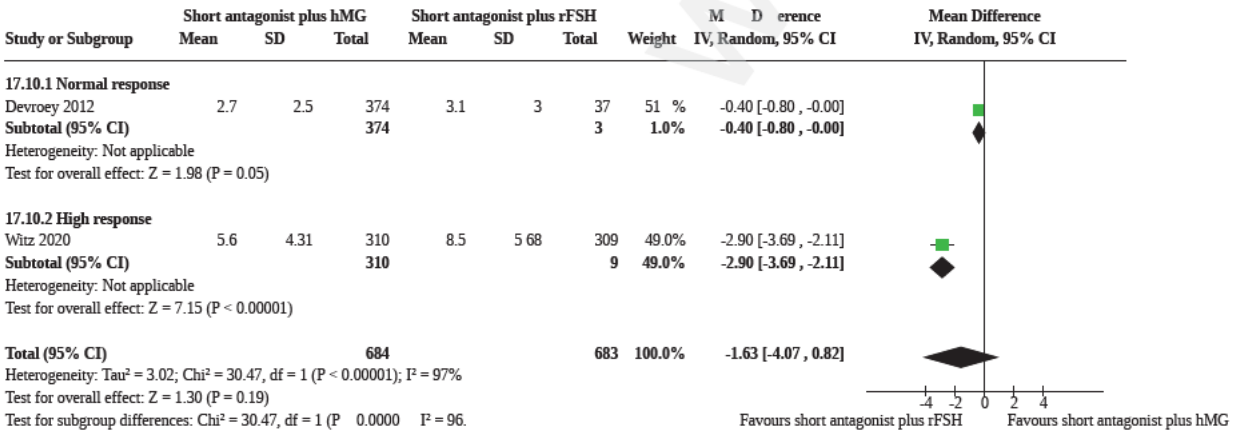
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Analysis 17.9. Comparison 17: Direct comparison: Short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH, Outcome 9: Cleavage embryo number



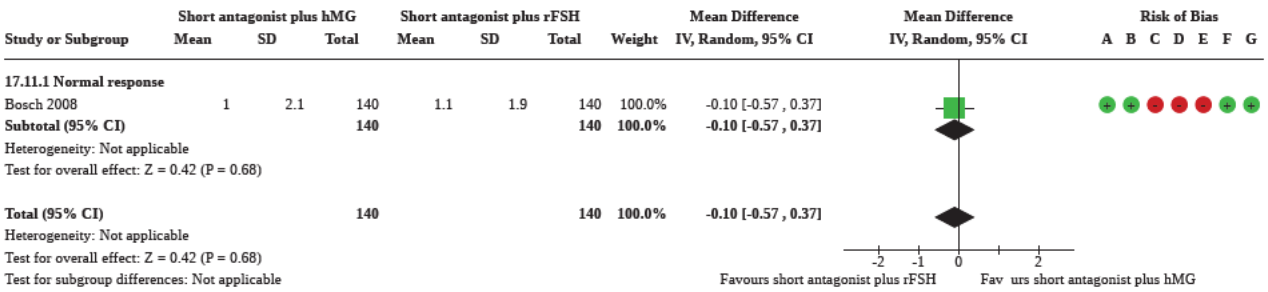
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 17.10. Comparison 17: Direct comparison: Short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH, Outcome 10: Blastocyst number



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Analysis 17.11. Comparison 17: Direct comparison: Short GnRH antagonist plus hMG versus short GnRH antagonist plus rFSH, Outcome 11: Frozen embryo number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

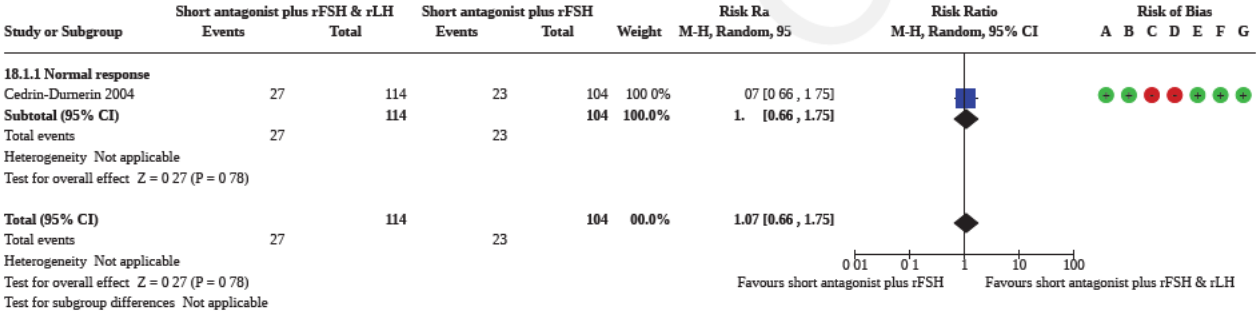
Comparison 18. Direct comparison: Short GnRH antagonist plus rFSH & rLH versus short GnRH antagonist plus rFSH

Outcome or subgroup title	No. of studies	No. of participants	Statistic l method	Effect size
18.1 Live birth	1	218	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.66, 1.75]
18.1.1 Normal response	1	218	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.66, 1.75]
18.2 OHSS	1	720	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.22, 2.96]
18.2.1 Normal response	1	720	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.22, 2.96]
18.3 Clinical pregnancy	2	287	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.57, 1.43]
18.3.1 Normal response	1	253	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.48]
18.3.2 Low response	1	34	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.14, 3.94]
18.4 Multiple pregnancy	1	253	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.03, 2.26]
18.4.1 Normal response	1	253	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.03, 2.26]
18.5 Miscarriage	2	471	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.50, 2.28]
18.5.1 Normal response	2	471	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.50, 2.28]
18.6 Ectopic	2	471	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.21, 2.85]
18.6.1 Normal response	2	471	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.21, 2.85]
18.7 Cancellation	4	1225	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.53, 1.37]
18.7.1 Normal response	3	1191	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.40, 1.63]
18.7.2 Low response	1	34	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.26, 2.19]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.8 Oocyte number	4	1225	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.40, -0.20]
18.8.1 Normal response	3	1191	Mean Difference (IV, Random, 95% CI)	-0.68 [-1.42, 0.06]
18.8.2 Low response	1	34	Mean Difference (IV, Random, 95% CI)	-1.30 [-2.90, 0.30]
18.9 Frozen embryo number	2	973	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.62, -0.07]
18.9.1 Normal response	2	973	Mean Difference (IV, Random, 95% C	-0.35 [-0.62, -0.07]

Analysis 18.1. Comparison 18: Direct comparison: Short nRH ntagonist plus rFSH & rLH versus short GnRH antagonist plus r SH, Outc me 1: Live birth

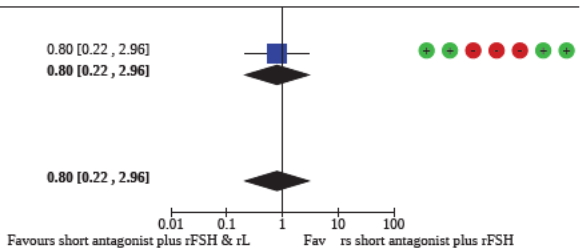


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 18.2. Comparison 18: Direct comparison: Short GnRH antagonist plus rFSH & rLH versus short GnRH antagonist plus rFSH, Outcome 2: OHSS

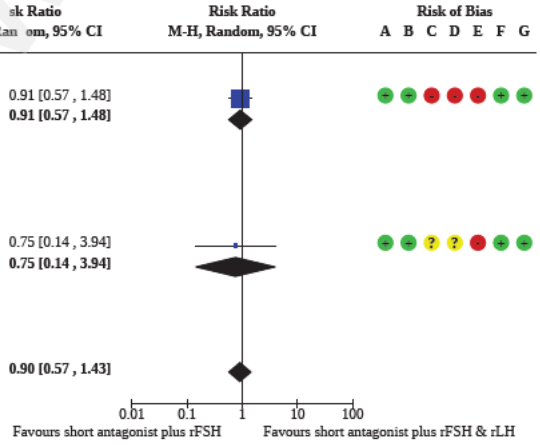
Study or Subgroup	Short antagonist plus rFSH & rLH Events	Total	Short antagonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
18.2.1 Normal response						
Bosch 2011	4	360	5	360	100.0%	0.80 [0.22 , 2.96]
Subtotal (95% CI)		**360**		**360**	**100.0%**	**0.80 [0.22 , 2.96]**
Total events:	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)		**360**		**360**	**100.0%**	**0.80 [0.22 , 2.96]**
Total events:	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 18.3. Comparison 18: Direct comparison: Short GnRH antagonist plus rFSH & rLH versus short GnRH antagonist plus rFSH Outcome 3: Clinical pregnancy

Study or Subgroup	Short antagonist plus rFSH & rLH Events	Total	Short antagonist plus rFSH Events	Total	Weight	sk Ratio Ran om, 95% CI
18.3.1 Normal response						
Konig 2013	25	125	28	128	92 3%	0.91 [0.57 , 1.48]
Subtotal (95% CI)		**125**		**128**	**3%**	**0.91 [0.57 , 1.48]**
Total events:	25		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
18.3.2 Low response						
Ramirez 2006	2	16	3	18	7.7%	0.75 [0.14 , 3.94]
Subtotal (95% CI)		**16**		**18**	**7.7%**	**0.75 [0.14 , 3.94]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
Total (95% CI)		**41**		**146**	**100.0%**	**0.90 [0.57 , 1.43]**
Total events:	27		31			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.8 ; I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.66)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.8 I² 0%						

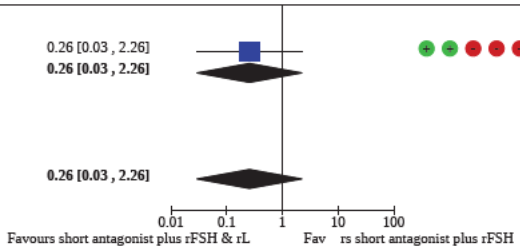


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (perf ance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bi)
(F) Selective reporting (reporting bias
(G) Other bias

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Analysis 18.4. Comparison 18: Direct comparison: Short GnRH antagonist plus rFSH & rLH versus short GnRH antagonist plus rFSH, Outcome 4: Multiple pregnancy

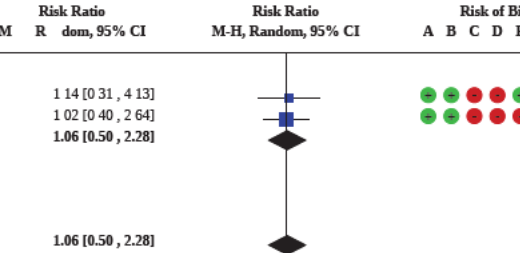
Study or Subgroup	Short antagonist plus rFSH & rLH Events	Total	Short antagonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
18.4.1 Normal response							
Konig 2013	1	125	4	128	100.0%	0.26 [0.03 , 2.26]	+ + - - - + +
Subtotal (95% CI)		**125**		**128**	**100.0%**	**0.26 [0.03 , 2.26]**	
Total events:	1		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.23 (P = 0.22)							
Total (95% CI)		**125**		**128**	**100.0%**	**0.26 [0.03 , 2.26]**	
Total events:	1		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.23 (P = 0.22)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 18.5. Comparison 18: Direct comparison: Short GnRH antagonist plus rFSH & rLH versus short GnRH antagonist plus rFSH, Outcome 5: Miscarriage

Study or Subgroup	Short antagonist plus rFSH & rLH Events	Total	Short antagonist plus rFSH Events	Total	Weight	M R dom, 95% CI	Risk of Bias A B C D E F G
18.5.1 Normal response							
Cedrin-Durnerin 2004	5	114	4	10	3 2%	1 14 [0 31 , 4 13]	+ + - - - + +
Konig 2013	8	125	8	128	4 8%	1 02 [0 40 , 2 64]	+ + - - - + +
Subtotal (95% CI)		**239**		**32**	**10**	**1.06 [0.50 , 2.28]**	
Total events	13		12				
Heterogeneity Tau² = 0 00; Chi² = 0 02, df = 1 (P = 0 90); I² = 0%							
Test for overall effect Z = 0 16 (P = 0 87)							
Total (95% CI)		**239**		**232**	**100.0%**	**1.06 [0.50 , 2.28]**	
Total events	13		12				
Heterogeneity Tau² = 0 00; Chi² = 0 02, df = 1 (P = 0 90); I² = 0%							
Test for overall effect Z = 0 16 (P = 0 87)							
Test for subgroup differences Not applicable							

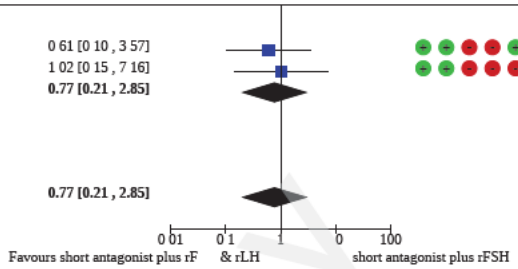


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performa bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 18.6. Comparison 18: Direct comparison: Short GnRH antagonist plus rFSH & rLH versus short GnRH antagonist plus rFSH, Outcome 6: Ectopic

Study or Subgroup	Short antagonist plus rFSH & rLH Events	Total	Short antagonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
18.6.1 Normal response						
Cedrin-Durnerin 2004	2	114	3	104	54 7%	0 61 [0 10 , 3 57]
Konig 2013	2	125	2	128	45 3%	1 02 [0 15 , 7 16]
Subtotal (95% CI)		**239**		232	**100.0%**	**0.77 [0.21 , 2.85]**
Total events	4		5			
Heterogeneity Tau² = 0 00; Chi² = 0 15, df = 1 (P = 0 70); I² = 0%						
Test for overall effect Z = 0 39 (P = 0 70)						
Total (95% CI)		**239**		232	**100.0%**	**0.77 [0.21 , 2.85]**
Total events	4		5			
Heterogeneity Tau² = 0 00; Chi² = 0 15, df = 1 (P = 0 70); I² = 0%						
Test for overall effect Z = 0 39 (P = 0 70)						
Test for subgroup differences Not applicable						



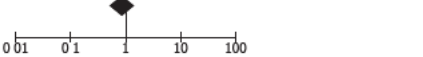


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 18.7. Comparison 18: Direct comparison: Short GnRH antagonist plus rFSH & rLH versus short GnRH antagonist p us rFSH, Outcome 7: Cancellation

Study or Subgroup	Short antagonist plus rFSH & rLH Events	Total	Short antagonist plus rFSH Events	Total	W h	R k Ratio M-H, Random, 95% CI
18.7.1 Normal response						
Bosch 2011	28	360	24	360	1 2%	1 17 [0 69 , 1 97]
Cedrin-Durnerin 2004	0	114	3	104		0 13 [0 01 , 2 50]
Konig 2013	9	125	15	1	28 9%	0 61 [0 28 , 1 35]
Subtotal (95% CI)		**599**		592	**6%**	**0.81 [0.40 , 1.63]**
Total events	37		42			
Heterogeneity Tau² = 0 16; Chi² = 3 50, df = 2 (P = 0 17); I² = 43%						
Test for overall effect Z = 0 60 (P = 0 55)						
18.7.2 Low response						
Ramirez 2006	4	16		18	17 4%	0 75 [0 26 , 2 19]
Subtotal (95% CI)		**16**		**18**	**17.4%**	**0.75 [0.26 , 2.19]**
Total events	4		6			
Heterogeneity Not applicable						
Test for overall effect Z = 0 53 (P = 0 60)						
Total (95% CI)		**6**		**610**	**100.0%**	**0.85 [0.53 , 1.37]**
Total events	41		48			
Heterogeneity Tau² = 0 04; Chi² = 3 61, df = 3 (P = 0 31); I² %						
Test for overall effect Z = 0 67 (P = 0 50)						
Test for subgroup differences Chi² = 0 01, df = 1 (P = 0 91), I² = 0%						

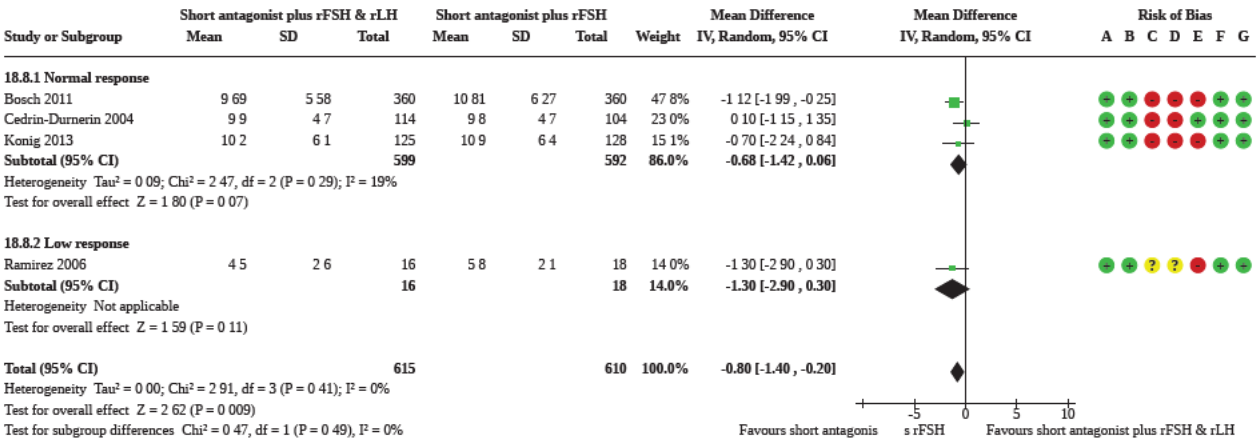




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bia
(C) Blinding of participants and person el (perfor nce bias)
(D) Blinding of outcome assessment (tection bias)
(E) Incomplete outcome d (attrition s)
(F) Selective reporting (porting bias)
(G) Other bias

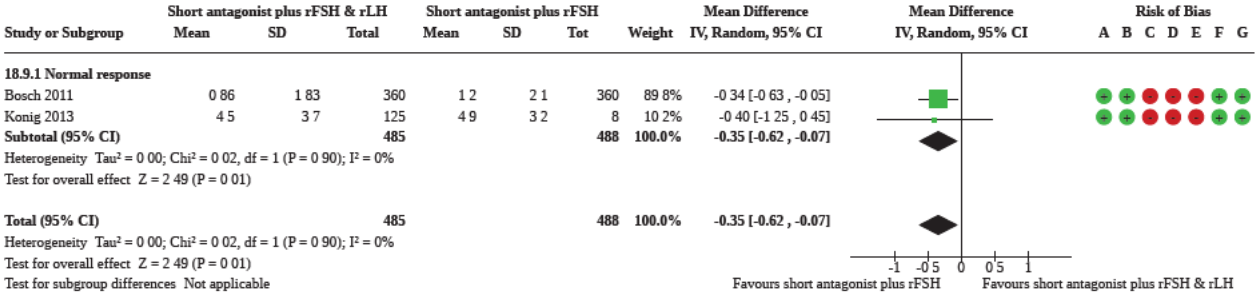
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Analysis 18.8. Comparison 18: Direct comparison: Short GnRH antagonist plus rFSH & rLH versus short GnRH antagonist plus rFSH, Outcome 8: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 18.9. Comparison 18: Direct comparison Short GnRH antagonist plus rFSH & rLH versus short GnRH antagonist plus rFSH Outcome 9: Frozen embryo number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection b
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

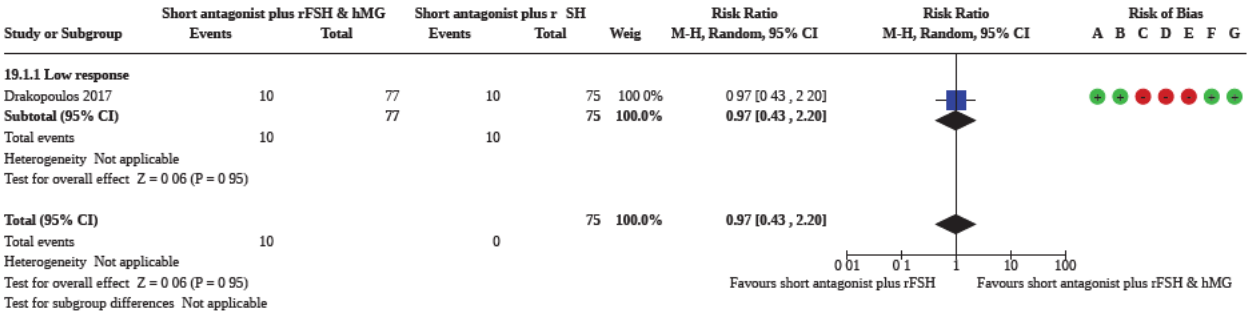
Comparison 19 Dire t comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus rFSH

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
19.1 Live birth	1	152	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.43, 2.20]
19.1.1 Low response	1	152	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.43, 2.20]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.2 Clinical pregnancy	1	152	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.42, 1.90]
19.2.1 Low response	1	152	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.42, 1.90]
19.3 Ongoing pregnancy	1	152	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.45, 2.11]
19.3.1 Low response	1	152	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.45, 2.11]
19.4 Cancellation	1	152	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.70, 4.01]
19.4.1 Low response	1	152	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.70, 4.01]
19.5 Oocyte number	1	152	Mean Difference (IV, Random, 95% CI)	0.00 [-0.92, 0.92]
19.5.1 Low response	1	152	Mean Difference (IV, Random, 95% CI)	0.00 [-0.92, 0.92]
19.6 Frozen embryo number	1	152	Mean Difference (IV, Random, 95% CI)	0.30 [-0.04, 0.64]
19.6.1 Low response	1	152	Mean Difference (IV, Random, 95% CI)	0.30 [-0.04, 0.64]

Analysis 19.1. Comparison 19: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antag nist plus rFSH, Outcome 1: Live birth

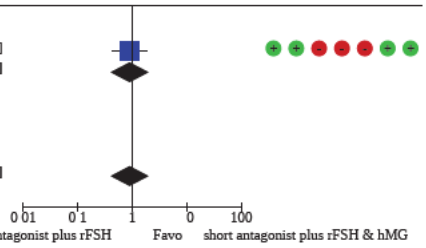


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (perfo nce bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition b)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 19.2. Comparison 19: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus rFSH, Outcome 2: Clinical pregnancy

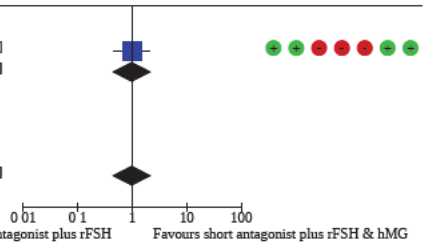
Study or Subgroup	Short antagonist plus rFSH & hMG Events	Total	Short antagonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
19.2.1 Low response						
Drakopoulos 2017	11	77	12	75	100 0%	0 89 [0 42 , 1 90]
Subtotal (95% CI)		77		75	**100.0%**	**0.89 [0.42 , 1.90]**
Total events	11		12			
Heterogeneity Not applicable						
Test for overall effect Z = 0 29 (P = 0 77)						
Total (95% CI)		77		75	**100.0%**	**0.89 [0.42 , 1.90]**
Total events	11		12			
Heterogeneity Not applicable						
Test for overall effect Z = 0 29 (P = 0 77)						
Test for subgroup differences Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 19.3. Comparison 19: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus rFSH, Outcome 3: Ongoing pregnancy

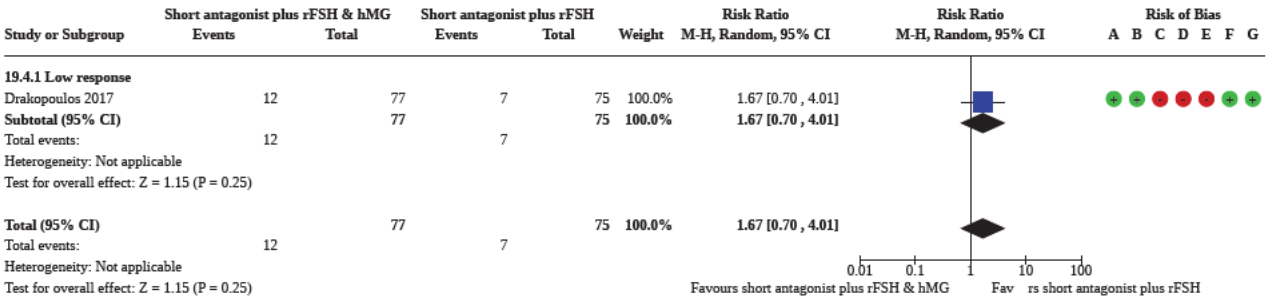
Study or Subgroup	Short antagonist plus rFSH & hMG Events	Total	Short antagonist plus rFSH Events	Total	Weight	Risk Rati H, Ra dom, 95% CI
19.3.1 Low response						
Drakopoulos 2017	11	77	11	75	100 0%	0 97 [0 45 , 2 11]
Subtotal (95% CI)		77		75	**00 %**	**0.97 [0.45 , 2.11]**
Total events	11		11			
Heterogeneity Not applicable						
Test for overall effect Z = 0 07 (P = 0 95)						
Total (95% CI)		77			**100.0%**	**0.97 [0.45 , 2.11]**
Total events	11		11			
Heterogeneity Not applicable						
Test for overall effect Z = 0 07 (P = 0 95)						
Test for subgroup differences Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance b s)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

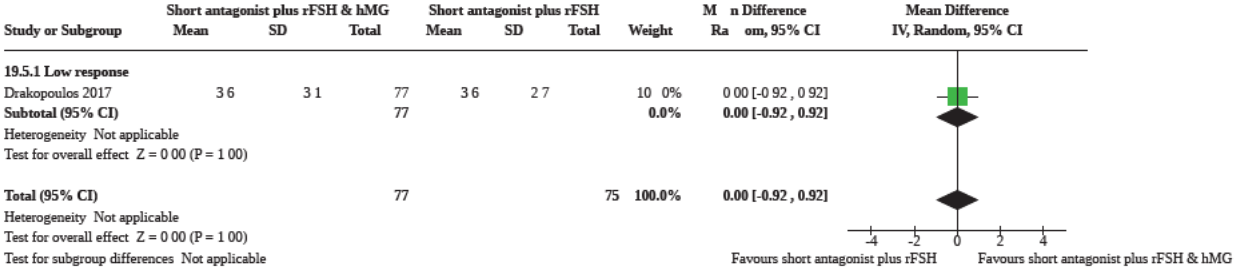
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Analysis 19.4. Comparison 19: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus rFSH, Outcome 4: Cancellation

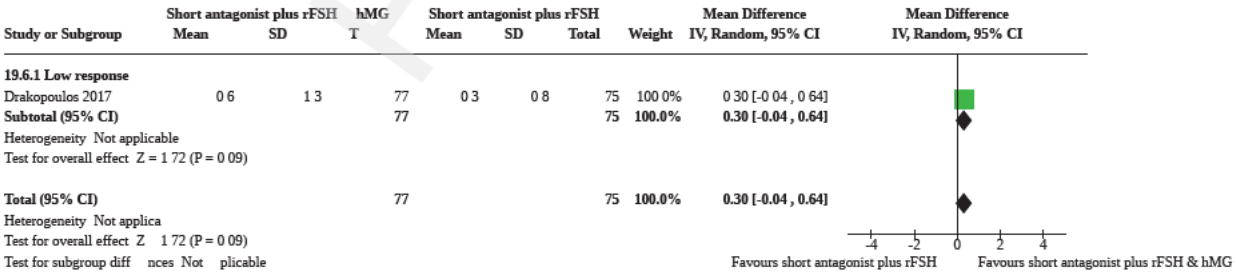


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 19.5. Comparison 19: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus rFSH, Outcome 5: Oocyte number



Analysis 19.6. Comparis n 19: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus sh rt GnRH an agonist plus rFSH, Outcome 6: Frozen embryo number



Comparison 20. Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus hMG

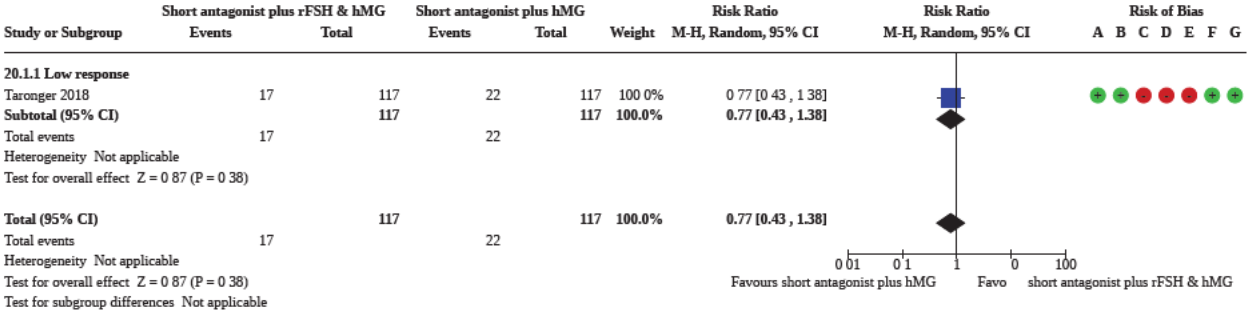
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Live birth	1	234	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.43, 1.38]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1.1 Low response	1	234	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.43, 1.38]
20.2 OHSS	1	234	Risk Ratio (M-H, Random, 95% CI)	Not estimable
20.2.1 Low response	1	234	Risk Ratio (M-H, Random, 95% CI)	Not estimable
20.3 Clinical pregnancy	1	234	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.48, 1.35]
20.3.1 Low response	1	234	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.48, 1.35]
20.4 Ongoing pregnancy	1	234	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.43, 1.38]
20.4.1 Low response	1	234	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.43, 1.38]
20.5 Miscarriage	1	234	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.38, 3.82]
20.5.1 Low response	1	234	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.38, 3.82]
20.6 Ectopic	1	234	Risk Ratio (M-H, Random, 95% CI)	Not estimable
20.6.1 Low response	1	234	Risk Ratio (M-H, Random, 95% CI)	Not estimable
20.7 Cancellation	1	234	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.19, 2.30]
20.7.1 Low response	1	234	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.19, 2.30]
20.8 Oocyte number	1	234	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.46, 0.06]
20.8.1 Low response	1	234	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.46, 0.06]
20.9 Cleavage embryo number	1	234	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.89, -0.11]
20.9.1 Low response	1	234	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.89, -0.11]

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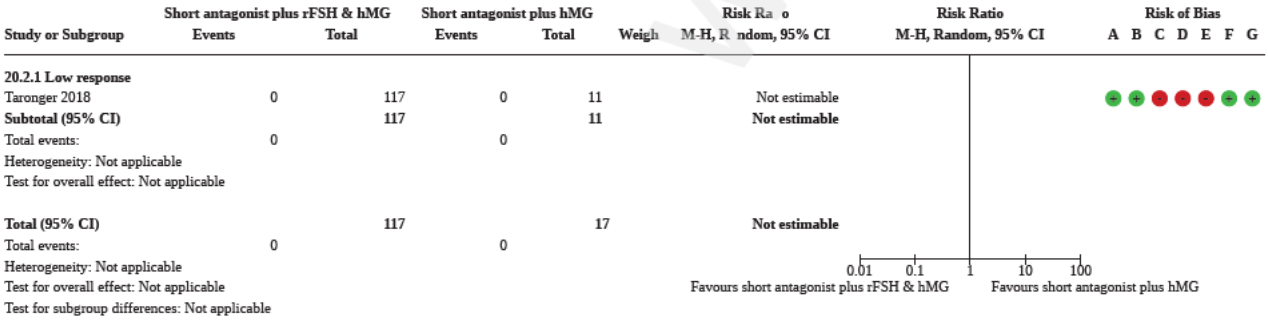
Analysis 20.1. Comparison 20: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus hMG, Outcome 1: Live birth



Study or Subgroup	Short antagonist plus rFSH & hMG Events	Total	Short antagonist plus hMG Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
20.1.1 Low response						
Taronger 2018	17	117	22	117	100 0%	0 77 [0 43 , 1 38]
Subtotal (95% CI)		117		117	**100.0%**	**0.77 [0.43 , 1.38]**
Total events	17		22			
Heterogeneity Not applicable						
Test for overall effect Z = 0 87 (P = 0 38)						
Total (95% CI)		117		117	**100.0%**	**0.77 [0.43 , 1.38]**
Total events	17		22			
Heterogeneity Not applicable						
Test for overall effect Z = 0 87 (P = 0 38)						
Test for subgroup differences Not applicable						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 20.2. Comparison 20: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus hMG, Outcome 2: OHSS



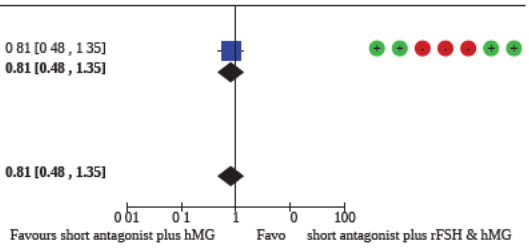
Study or Subgroup	Short antagonist plus rFSH & hMG Events	Total	Short antagonist plus hMG Events	Total	Weigh	Risk Ra o M-H, R ndom, 95% CI
20.2.1 Low response						
Taronger 2018	0	117	0	11		Not estimable
Subtotal (95% CI)		117		11		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		117		17		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance as)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 20.3. Comparison 20: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus hMG, Outcome 3: Clinical pregnancy

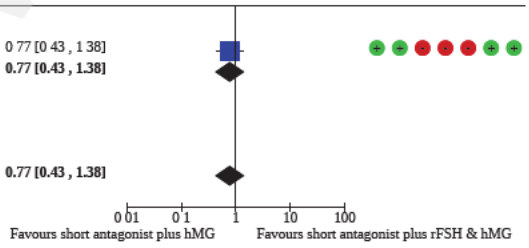
Study or Subgroup	Short antagonist plus rFSH & hMG Events	Total	Short antagonist plus hMG Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
20.3.1 Low response						
Taronger 2018	21	117	26	117	100 0%	0 81 [0 48 , 1 35]
Subtotal (95% CI)		**117**		**117**	**100.0%**	**0.81 [0.48 , 1.35]**
Total events	21		26			
Heterogeneity Not applicable						
Test for overall effect Z = 0 81 (P = 0 42)						
Total (95% CI)		**117**		**117**	**100.0%**	**0.81 [0.48 , 1.35]**
Total events	21		26			
Heterogeneity Not applicable						
Test for overall effect Z = 0 81 (P = 0 42)						
Test for subgroup differences Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 20.4. Comparison 20: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus hMG, Outcome 4: Ongoing pregnancy

Study or Subgroup	Short antagonist plus rFSH & hMG Events	Total	Short antagonist plus hMG Events	Total	Weight	Risk Rati H, Ra dom, 95% CI
20.4.1 Low response						
Taronger 2018	17	117	22	117	100 0%	0 77 [0 43 , 1 38]
Subtotal (95% CI)		**117**		**117**	**00 %**	**0.77 [0.43 , 1.38]**
Total events	17		22			
Heterogeneity Not applicable						
Test for overall effect Z = 0 87 (P = 0 38)						
Total (95% CI)		**117**			**100.0%**	**0.77 [0.43 , 1.38]**
Total events	17		22			
Heterogeneity Not applicable						
Test for overall effect Z = 0 87 (P = 0 38)						
Test for subgroup differences Not applicable						

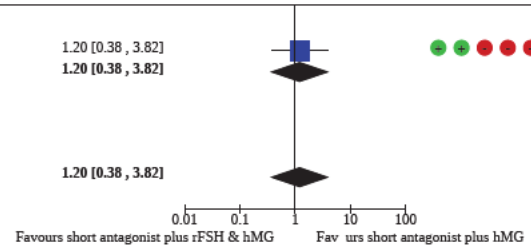


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance b s)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 20.5. Comparison 20: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus hMG, Outcome 5: Miscarriage

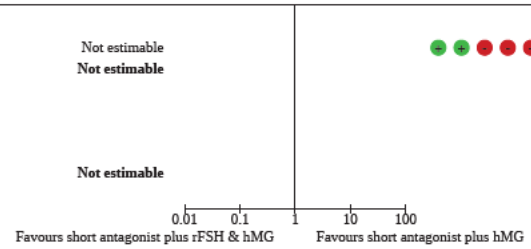
Study or Subgroup	Short antagonist plus rFSH & hMG Events	Total	Short antagonist plus hMG Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
20.5.1 Low response							
Taronger 2018	6	117	5	117	100.0%	1.20 [0.38 , 3.82]	+ + - - - + +
Subtotal (95% CI)		**117**		**117**	**100.0%**	**1.20 [0.38 , 3.82]**	
Total events:	6		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.31 (P = 0.76)							
Total (95% CI)		**117**		**117**	**100.0%**	**1.20 [0.38 , 3.82]**	
Total events:	6		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.31 (P = 0.76)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 20.6. Comparison 20: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus hMG, Outcome 6: Ectopic

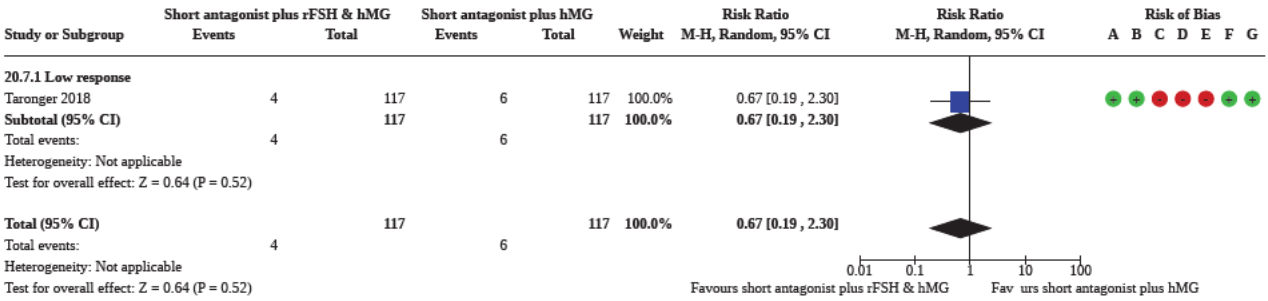
Study or Subgroup	Short antagonist plus rFSH & hMG Events	Total	Short antagonist plus hMG Events	Total	Weight	Risk Ratio H R dom, 95% CI	Risk of Bias A B C D E F G
20.6.1 Low response							
Taronger 2018	0	117	0	11		Not estimable	+ + - - - + +
Subtotal (95% CI)		**117**		**117**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**117**		**7**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performanc bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

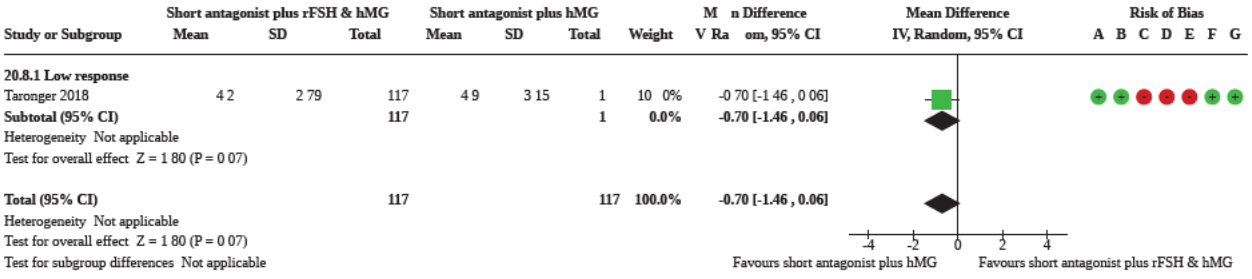
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Analysis 20.7. Comparison 20: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus hMG, Outcome 7: Cancellation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

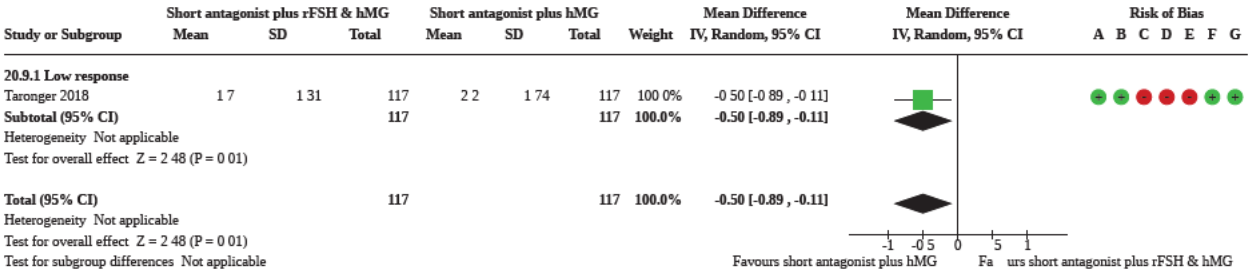
Analysis 20.8. Comparison 20: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus hMG, Outcome 8: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 20.9. Comparison 20: Direct comparison: Short GnRH antagonist plus rFSH & hMG versus short GnRH antagonist plus hMG, Outcome 9: Cleavage embryo number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

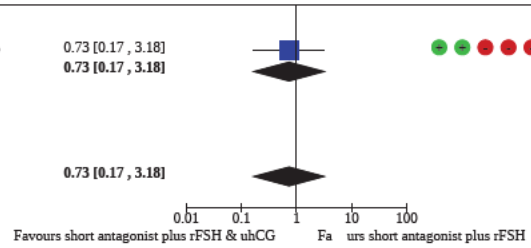
Comparison 21. Direct comparison: Short GnRH antagonist plus rFSH & hCG versus short GnRH antagonist plus rFSH

Outcome or subgroup title	No. of studies	No. of participants	St tistic l method	Effect size
21.1 OHSS	1	217	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.17, 3.18]
21.1.1 Normal response	1	217	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.17, 3.18]
21.2 Clinical pregnancy	1	217	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.12, 2.16]
21.2.1 Normal response	1	217	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.12, 2.16]
21.3 Cancellation	1	2 7	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.17, 3.18]
21.3.1 Normal response	1	217	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.17, 3.18]
21.4 Oocyte number	1	217	Mean Difference (IV, Random, 95% CI)	-1.40 [-1.60, -1.20]
21.4.1 Normal response	1	217	Mean Difference (IV, Random, 95% CI)	-1.40 [-1.60, -1.20]

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Analysis 21.1. Comparison 21: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH, Outcome 1: OHSS

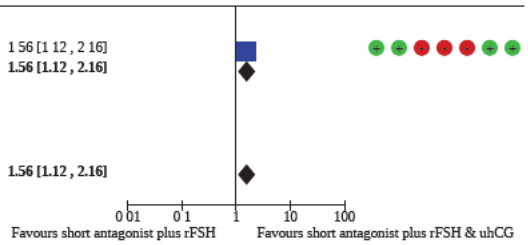
Study or Subgroup	Short antagonist plus rFSH & uhCG Events	Total	Short antagonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
21.1.1 Normal response							
Serafini 2006	3	110	4	107	100.0%	0.73 [0.17 , 3.18]	+ + - - - + +
Subtotal (95% CI)		**110**		**107**	**100.0%**	**0.73 [0.17 , 3.18]**	
Total events:	3		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.42 (P = 0.67)							
Total (95% CI)		**110**		**107**	**100.0%**	**0.73 [0.17 , 3.18]**	
Total events:	3		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.42 (P = 0.67)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 21.2. Comparison 21: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH, Outcome 2: Clinical pregnancy

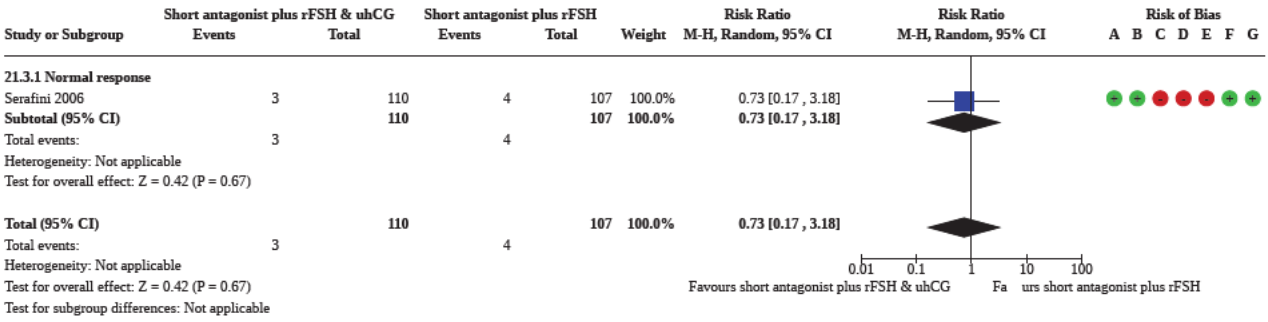
Study or Subgroup	Short antagonist plus rFSH & uhCG Events	Total	Short antagonist plus rFSH Events	Total	Weight	sk Ratio Ran om, 95% CI	Risk of Bias A B C D E F G
21.2.1 Normal response							
Serafini 2006	56	110	35	107	100 0	1 56 [1 12 , 2 16]	+ + - - - + +
Subtotal (95% CI)		**110**		**107**	**00 %**	**1.56 [1.12 , 2.16]**	
Total events	56		35				
Heterogeneity Not applicable							
Test for overall effect Z = 2 64 (P = 0 008)							
Total (95% CI)		**110**		**1**	**100.0%**	**1.56 [1.12 , 2.16]**	
Total events	56		35				
Heterogeneity Not applicable							
Test for overall effect Z = 2 64 (P = 0 008)							
Test for subgroup differences Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance b s)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

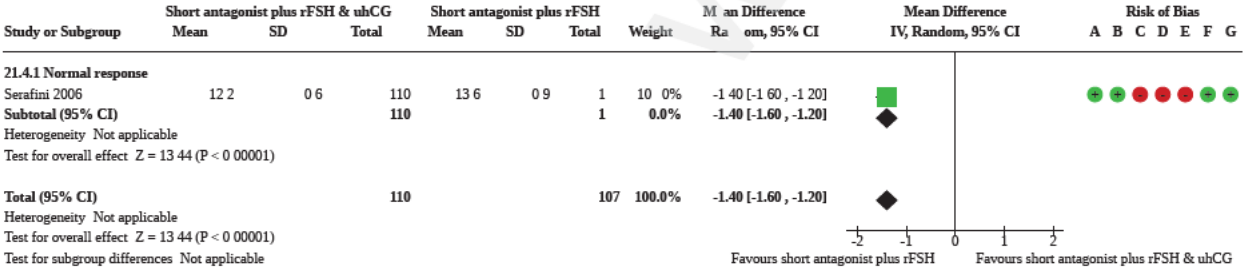
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Analysis 21.3. Comparison 21: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH, Outcome 3: Cancellation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 21.4. Comparison 21: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH, Outcome 4: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 22. Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH & rLH

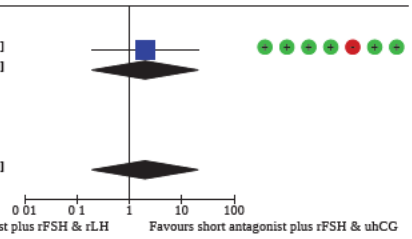
Outcome or subgroup title	No. of s udies	No. of partici-pants	Statistical method	Effect size
22.1 Live birth	1	50	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.19, 20.67]
22.1.1 Low response	1	50	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.19, 20.67]
22.2 Clinical pregnancy	1	50	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.15, 6.55]
22.2.1 Low response	1	50	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.15, 6.55]
22.3 Miscarriage	1	50	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.81]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.3.1 Low response	1	50	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.81]
22.4 Cancellation	1	50	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.12, 1.47]
22.4.1 Low response	1	50	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.12, 1.47]
22.5 Oocyte number	1	50	Mean Difference (IV, Random, 95% CI)	1.50 [-0.64, 3.64]
22.5.1 Low response	1	50	Mean Difference (IV, Random 95% C)	1.50 [-0.64, 3.64]

Analysis 22.1. Comparison 22: Direct comparison: Short Gn H antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH & rLH, Outc me 1: Live birth

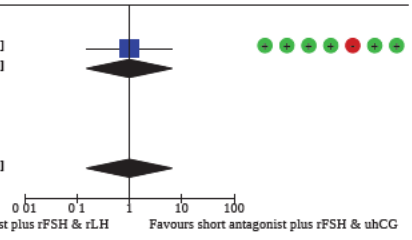
Study or Subgroup	Short antagonist plus rFSH & uhCG Events	Total	Short antagonist plus rFSH & rLH Events	Total	Weight	Risk atio M-H, Rando 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
22.1.1 Low response								
Mak 2017	2	25	1	25	100 0%	2 00 [0 19 , 20 67]		
Subtotal (95% CI)		25		25	**100.0%**	**2.00 [0.19 , 20.67]**		
Total events	2		1					
Heterogeneity Not applicable								
Test for overall effect Z = 0 58 (P = 0 56)								
Total (95% CI)		25		25	**100.0**	**00 [0.19 , 20.67]**		
Total events	2		1					
Heterogeneity Not applicable								
Test for overall effect Z = 0 58 (P = 0 56)								
Test for subgroup differences Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 22.2. Compa ison 22: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH & rLH, Outcome 2: Clinical pregnancy

Study or Subgroup	Short antagonist plus rFSH & uhCG Events	Total	Short antagonist plus rFSH & rLH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
22.2.1 Low response								
Mak 2017	2	25	2	25	100 0%	1 00 [0 15 , 6 55]		
Subtotal (95% CI)		25		25	**100.0%**	**1.00 [0.15 , 6.55]**		
Total events			2					
Heterogeneity Not applicable								
Test for overall effect Z = 0 00 (P = 1 0								
Total (95% CI)		25		25	**100.0%**	**1.00 [0.15 , 6.55]**		
Total events	2		2					
Heterogeneity Not ap able								
Test for overall effect Z = 1 00)								
Test for subgroup differences N applicable								

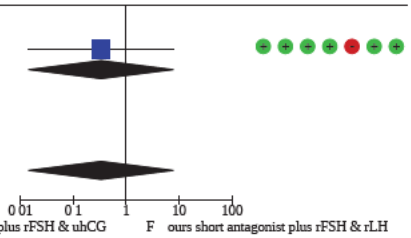


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 22.3. Comparison 22: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH & rLH, Outcome 3: Miscarriage

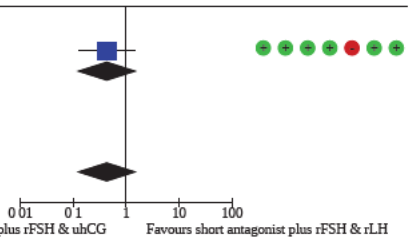
Study or Subgroup	Short antagonist plus rFSH & uhCG Events	Total	Short antagonist plus rFSH & rLH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
22.3.1 Low response						
Mak 2017	0	25	1	25	100 0%	0 33 [0 01 , 7 81]
Subtotal (95% CI)		25		25	**100.0%**	**0.33 [0.01 , 7.81]**
Total events	0		1			
Heterogeneity Not applicable						
Test for overall effect Z = 0 68 (P = 0 49)						
Total (95% CI)		25		25	**100.0%**	**0.33 [0.01 , 7.81]**
Total events	0		1			
Heterogeneity Not applicable						
Test for overall effect Z = 0 68 (P = 0 49)						
Test for subgroup differences Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 22.4. Comparison 22: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH & rLH, Outcome 4: Cancellation

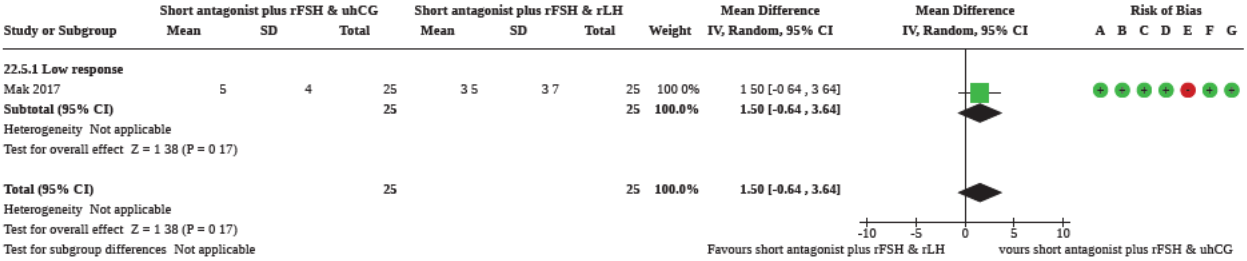
Study or Subgroup	Short antagonist plus rFSH & uhCG Events	Total	Short antagonist plus rFSH & rLH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
22.4.1 Low response						
Mak 2017	3	25	7		100 %	0 43 [0 12 , 1 47]
Subtotal (95% CI)		25		5	1 .0%	**0.43 [0.12 , 1.47]**
Total events	3		7			
Heterogeneity Not applicable						
Test for overall effect Z = 1 35 (P = 0 18)						
Total (95% CI)		25		25	**00.0%**	**0.43 [0.12 , 1.47]**
Total events	3		7			
Heterogeneity Not applicable						
Test for overall effect Z = 1 35 (P = 0 18)						
Test for subgroup differences Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 22.5. Comparison 22: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH & rLH, Outcome 5: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

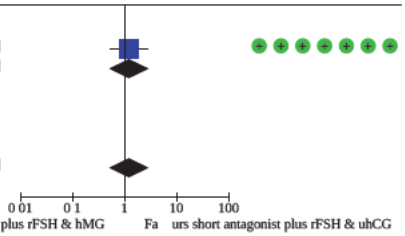
Comparison 23. Direct comparison: Short GnRH antagonist plus rFSH uhCG versus short GnRH antagonist plus rFSH & hMG

Outcome or subgroup title	No. of studies	No. of participants	Statis ical method	Effect size
23.1 Live birth	1	105	Risk R tio (M-H, Random, 95% CI)	1.22 [0.54, 2.76]
23.1.1 Normal response	1	105	R k Ratio (M-H, Random, 95% CI)	1.22 [0.54, 2.76]
23.2 Clinical pregnancy	1	105	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.74, 3.39]
23.2.1 Normal response	1	105	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.74, 3.39]
23.3 Ongoing pregnancy	1	105	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.59, 3.21]
23.3.1 Normal response	1	105	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.59, 3.21]
23.4 Oocyte number	1	105	Mean Difference (IV, Random, 95% CI)	-0.40 [-3.21, 2.41]
23.4.1 Normal response	1	105	Mean Difference (IV, Random, 95% CI)	-0.40 [-3.21, 2.41]

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Analysis 23.1. Comparison 23: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH & hMG, Outcome 1: Live birth

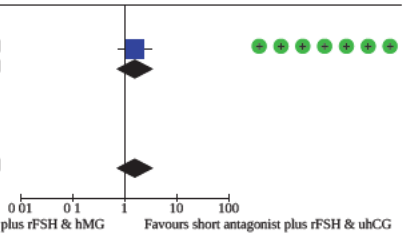
Study or Subgroup	Short antagonist plus rFSH & uhCG Events	Total	Short antagonist plus rFSH & hMG Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
23.1.1 Normal response						
Decleer 2020	10	50	9	55	100 0%	1 22 [0 54 , 2 76]
Subtotal (95% CI)		**50**		**55**	**100.0%**	**1.22 [0.54 , 2.76]**
Total events	10		9			
Heterogeneity Not applicable						
Test for overall effect Z = 0 48 (P = 0 63)						
Total (95% CI)		**50**		**55**	**100.0%**	**1.22 [0.54 , 2.76]**
Total events	10		9			
Heterogeneity Not applicable						
Test for overall effect Z = 0 48 (P = 0 63)						
Test for subgroup differences Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 23.2. Comparison 23: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH & hMG, Outcome 2: Clinical pregnancy

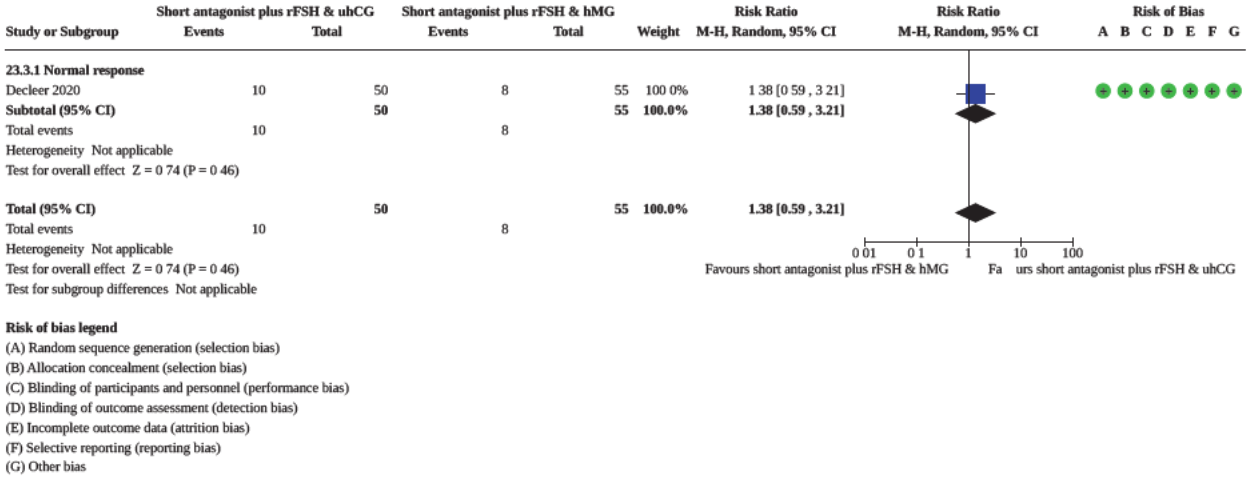
Study or Subgroup	Short antagonist plus rFSH & uhCG Events	Total	Short antagonist plus rFSH & hMG Events	Total	Weight	Risk atio M H, Ran 95% CI
23.2.1 Normal response						
Decleer 2020	13	50	9	55	%	1 59 [0 74 , 3 39]
Subtotal (95% CI)		**50**		**5**	**100 %**	**1.59 [0.74 , 3.39]**
Total events	13		9			
Heterogeneity Not applicable						
Test for overall effect Z = 1 20 (P = 0 23)						
Total (95% CI)		**50**		**55**	**00.0%**	**1.59 [0.74 , 3.39]**
Total events	13		9			
Heterogeneity Not applicable						
Test for overall effect Z = 1 20 (P = 0 23)						
Test for subgroup differences Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

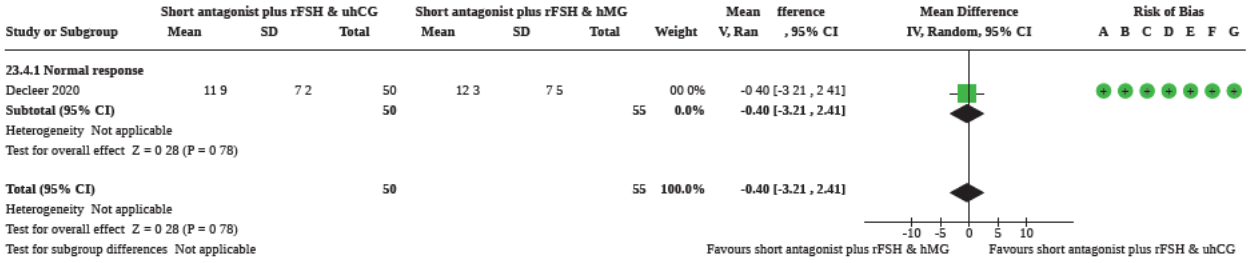
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Analysis 23.3. Comparison 23: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH & hMG, Outcome 3: Ongoing pregnancy



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 23.4. Comparison 23: Direct comparison: Short GnRH antagonist plus rFSH & uhCG versus short GnRH antagonist plus rFSH & hMG, Outcome 4: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

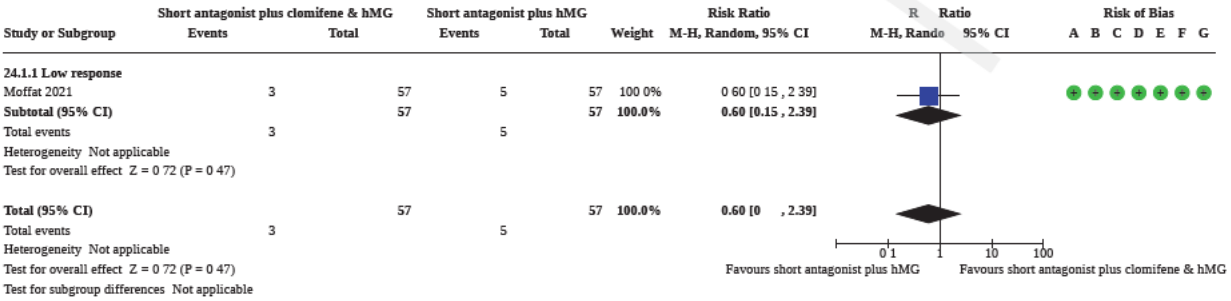
Comparison 24. Direct comparison: Sh rt GnRH antagonist plus clomifene & hMG versus short GnRH antagonist plus hMG

Outcome or subgroup title	No of st dies	No. of partici-pants	Statistical method	Effect size
24.1 Live birth	1	114	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.15, 2.39]
24.1.1 Low response	1	114	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.15, 2.39]
24.2 Miscarriage	1	114	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.20, 2.24]
24.2.1 Low response	1	114	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.20, 2.24]
24.3 Oocyte number	1	114	Mean Difference (IV, Random, 95% CI)	0.32 [0.05, 0.59]
24.3.1 Low response	1	114	Mean Difference (IV, Random, 95% CI)	0.32 [0.05, 0.59]

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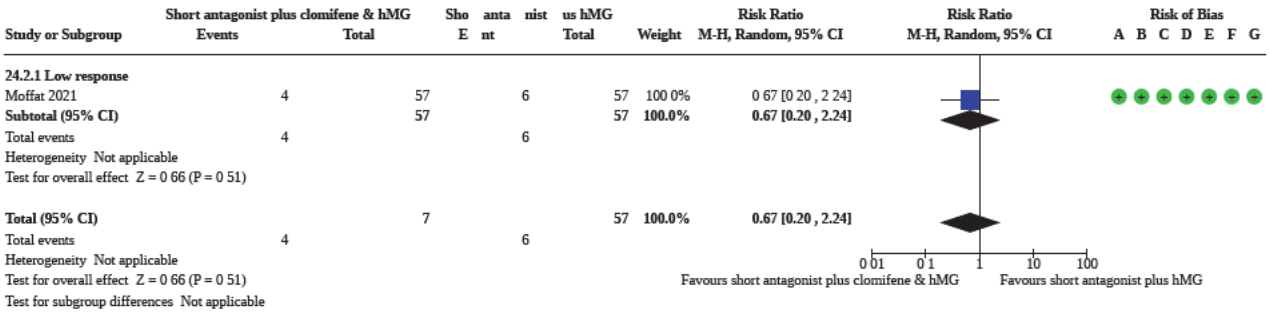
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.4 Blastocyst number	1	114	Mean Difference (IV, Random, 95% CI)	0.04 [-0.10, 0.18]
24.4.1 Low response	1	114	Mean Difference (IV, Random, 95% CI)	0.04 [-0.10, 0.18]

Analysis 24.1. Comparison 24: Direct comparison: Short GnRH antag nist plus clomifene & hMG versus short GnRH antagonist plus hMG, Outcome 1: L ve birth



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

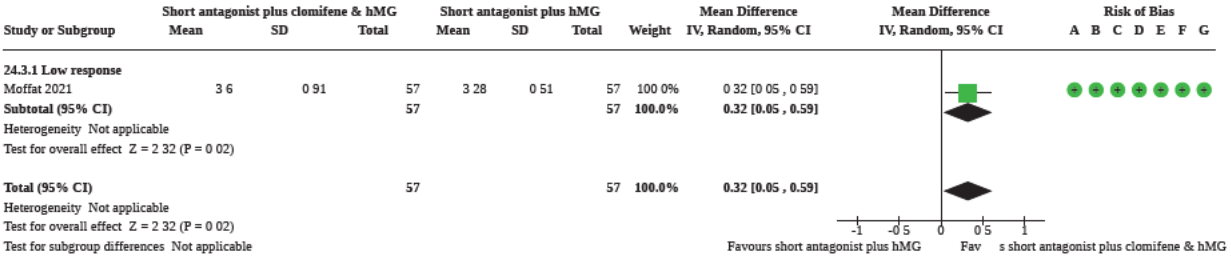
Analysis 24.2. Comparison 24: Dir ct comparison: Short GnRH antagonist plus clomifene & hMG versus short GnRH tagonist plus hMG, Outcome 2: Miscarriage



Risk of bias legend
(A) Random sequence generation (sele on bias)
(B) Allocation concealment election b)
(C) Blinding of participa s and personnel (f nce bias)
(D) Blinding of outco assessme (detection bias)
(E) Incomplete outc data (at ion bias)
(F) Selective reporting (re g bias)
(G) Other bias

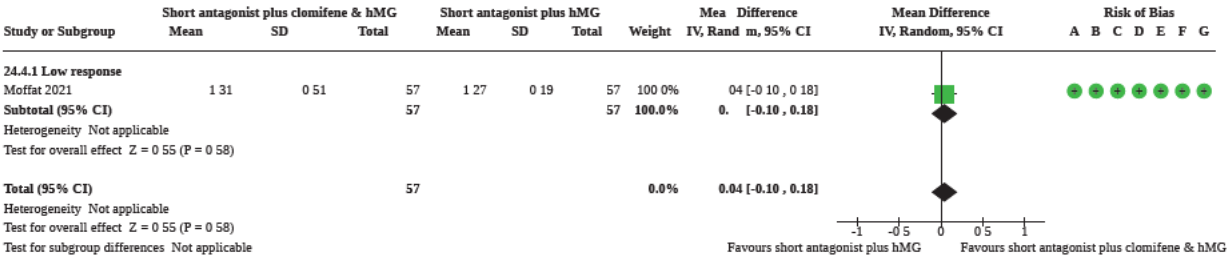
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Analysis 24.3. Comparison 24: Direct comparison: Short GnRH antagonist plus clomifene & hMG versus short GnRH antagonist plus hMG, Outcome 3: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 24.4. Comparison 24: Direct comparison: Short Gn H antagonist plus clomifene & hMG versus short GnRH antagonist plus hMG, O t ome 4: Blastocyst number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

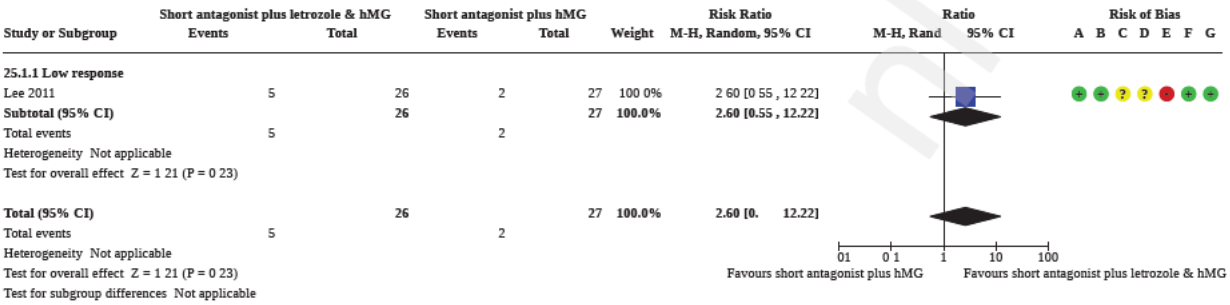
Comparison 25. Direct comparis n: hort GnRH antagonist plus letrozole & hMG versus short GnRH antagonist plus hMG

Outcome or subgroup title	No. o studies	No. of partici-pants	Statistical method	Effect size
25.1 Live birth	1	53	Risk Ratio (M-H, Random, 95% CI)	2.60 [0.55, 12.22]
25.1.1 Low response	1	53	Risk Ratio (M-H, Random, 95% CI)	2.60 [0.55, 12.22]
25.2 Ongoing pregnan cy	1	53	Risk Ratio (M-H, Random, 95% CI)	2.60 [0.55, 12.22]
25.2.1 Low response	1	53	Risk Ratio (M-H, Random, 95% CI)	2.60 [0.55, 12.22]
25.3 Miscarriage	1	53	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.62]
25.3.1 Low response	1	53	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.62]

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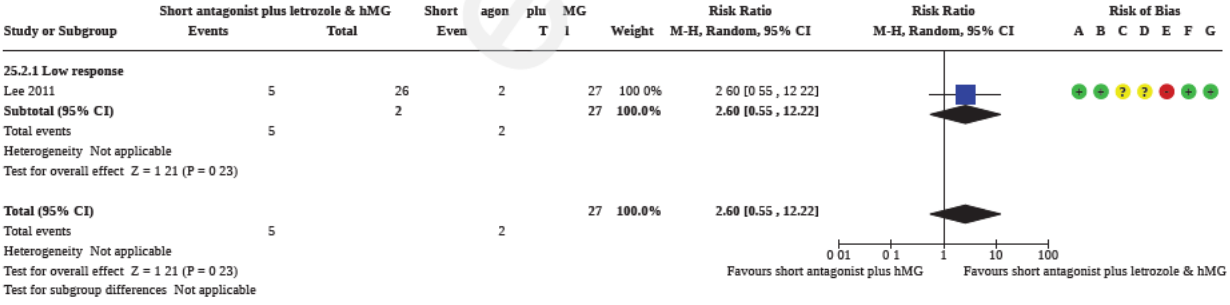
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.4 Cancellation	1	53	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.42, 10.39]
25.4.1 Low response	1	53	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.42, 10.39]

Analysis 25.1. Comparison 25: Direct comparison: Short GnRH antag nist plus letrozole & hMG versus short GnRH antagonist plus hMG, Outcome 1: Live birth



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

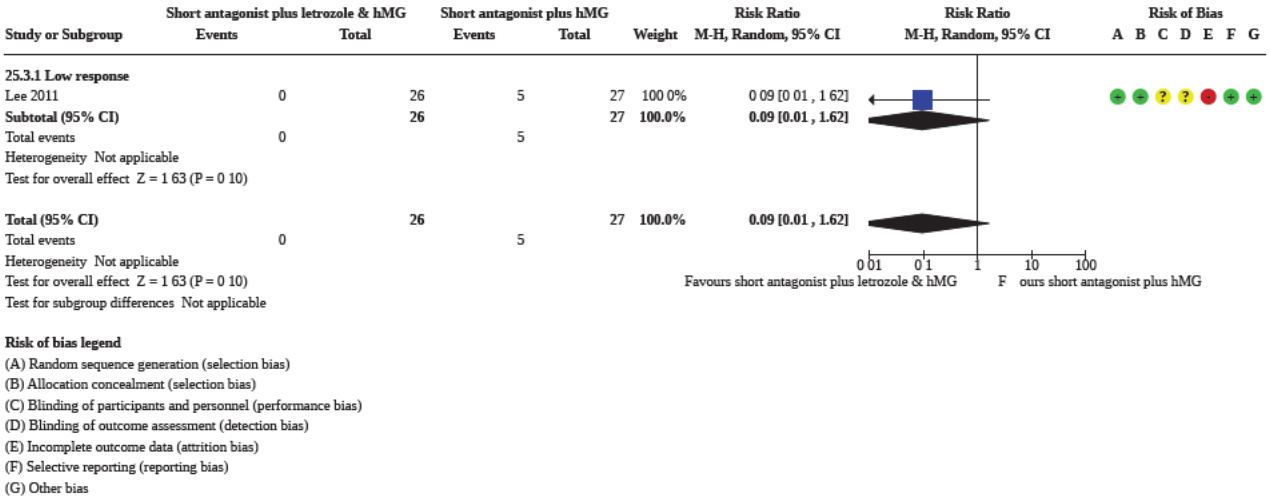
Analysis 25.2. Comparison 25: Direct comparison: Short GnRH antagonist plus letrozole & hMG versus short GnRH antagonis plus hMG, Outcome 2: Ongoing pregnancy



Risk of bias legend
(A) Random sequence generation (selec on bias)
(B) Allocation concealment (ection b
(C) Blinding of participan and personnel (form bias)
(D) Blinding of outcom ssessment detection bias)
(E) Incomplete outco data (attr n bias)
(F) Selective reporting (tin bias)
(G) Other bias

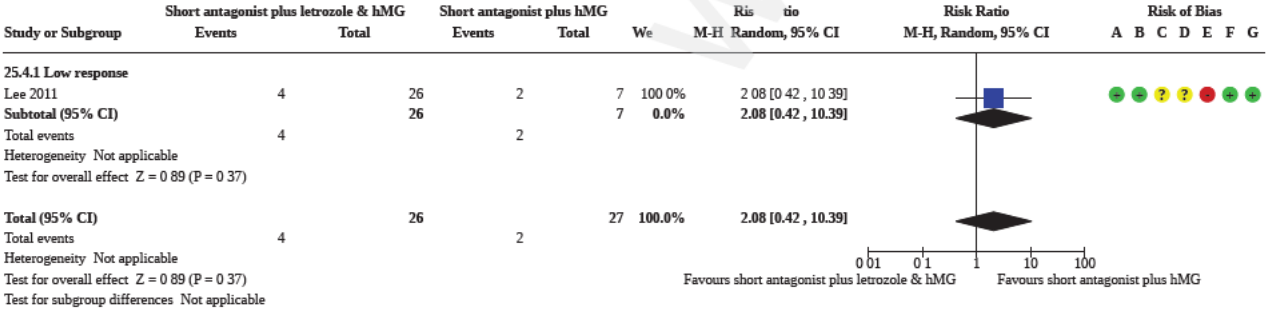
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Analysis 25.3. Comparison 25: Direct comparison: Short GnRH antagonist plus letrozole & hMG versus short GnRH antagonist plus hMG, Outcome 3: Miscarriage



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 25.4. Comparison 25: Direct comparison: Short GnRH antagonist plus letrozole & hMG versus short GnRH antagonist plus hMG, Outcome 4: Cancellation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bi
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

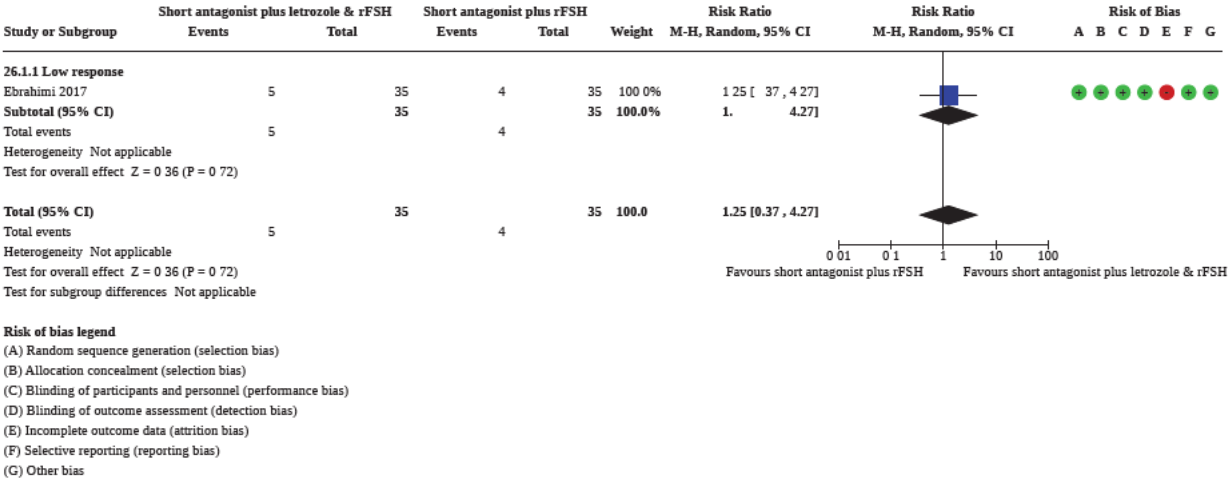
Comparison 26. Direct comparison: Short GnRH antagonist plus letrozole & rFSH versus short GnRH antagonist plus rFSH

Outcome or subg oup title	No f studies	No. of partici-pants	Statistical method	Effect size
26.1 Clinical pregnancy	1	70	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.37, 4.27]
26.1.1 Low response	1	70	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.37, 4.27]
26.2 Ongoing pregnancy	1	159	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.49, 1.29]
26.2.1 Normal response	1	159	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.49, 1.29]

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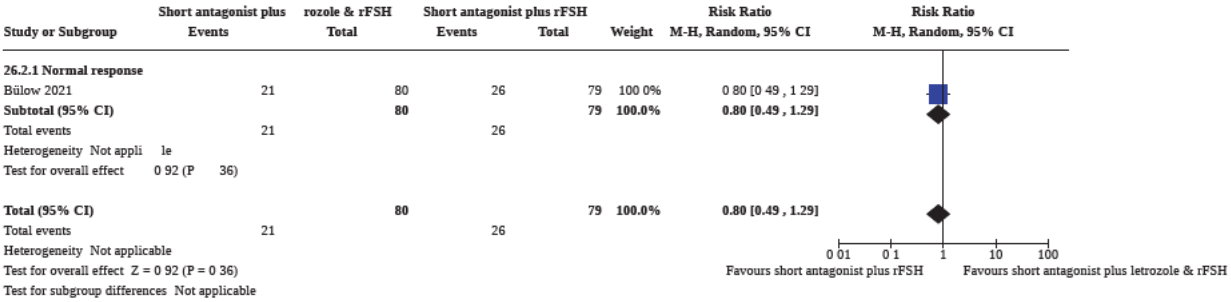
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.3 Cancellation	2	229	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.37, 1.66]
26.3.1 Normal response	1	159	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.15, 2.40]
26.3.2 Low response	1	70	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.36, 2.15]
26.4 Oocyte number	2	229	Mean Difference (IV, Random, 95% CI)	0.22 [-0.32, 0.77]
26.4.1 Normal response	1	159	Mean Difference (IV, Random, 95% CI)	0.30 [-0.87, 1.47]
26.4.2 Low response	1	70	Mean Difference (IV, Random, 95% CI)	0.20 [-0.42, 0.82]

Analysis 26.1. Comparison 26: Direct comparison: Sho t GnRH a tagonist plus letrozole & rFSH versus short GnRH antagonist plus rFSH, O tcome 1: Clinical pregnancy



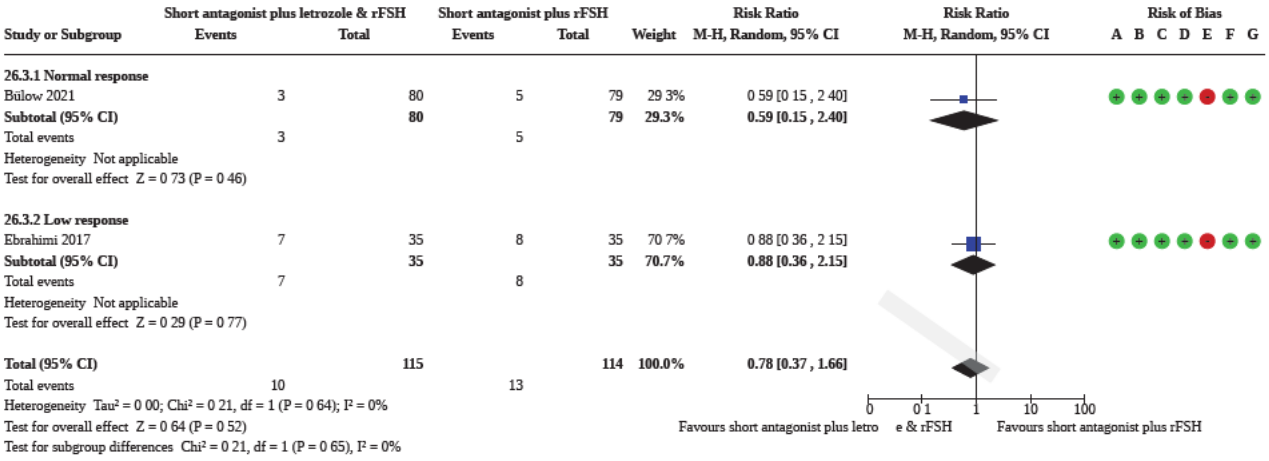
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 26.2. Compa ison 26: Direct comparison: Short GnRH antagonist plus letrozole & rFSH versus shor GnRH antagonist plus rFSH, Outcome 2: Ongoing pregnancy



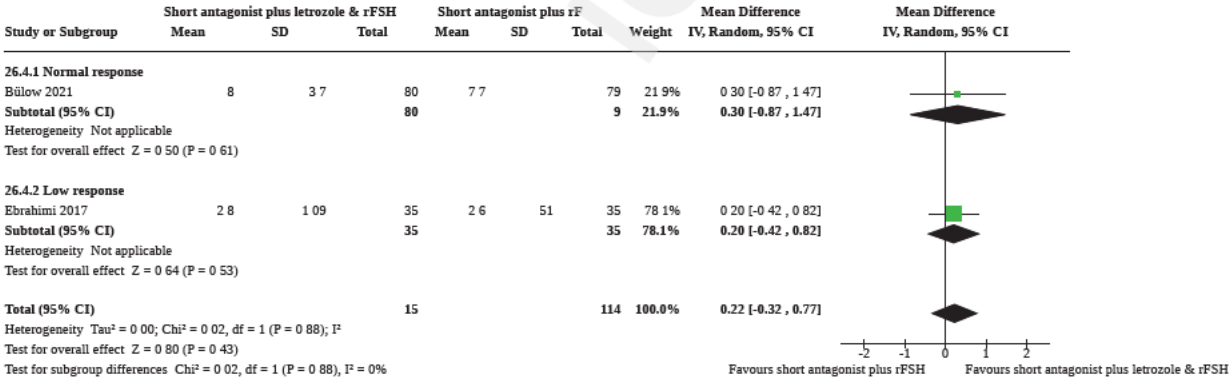
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Analysis 26.3. Comparison 26: Direct comparison: Short GnRH antagonist plus letrozole & rFSH versus short GnRH antagonist plus rFSH, Outcome 3: Cancellation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 26.4. Comparison 26: Direct comparison: Short GnRH antagonist plus letrozole & rFSH versus short GnRH antagonist plus rFSH, Outcome 4: Oocyte number



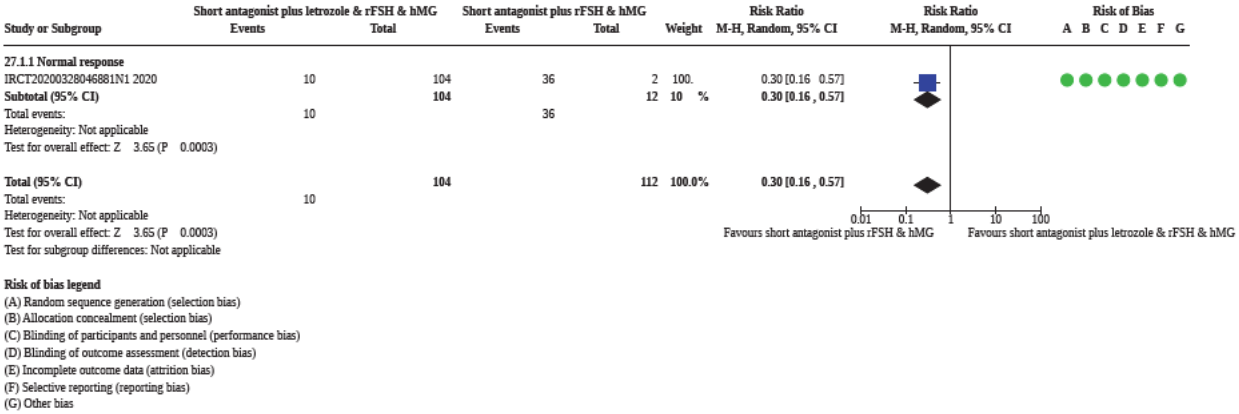
Comparison 27. Direct comparison: Short GnRH antagonist plus letrozole, rFSH & hMG versus short GnRH antagonist plus rFSH & hMG

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.1 Clinical pregnancy	1	216	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.16, 0.57]
27.1.1 Normal response	1	216	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.16, 0.57]
27.2 Miscarriage	1	216	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.86]
27.2.1 Normal response	1	216	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.86]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.3 Ectopic	1	216	Risk Ratio (M-H, Random, 95% CI)	Not estimable
27.3.1 Normal response	1	216	Risk Ratio (M-H, Random, 95% CI)	Not estimable
27.4 Cancellation	1	216	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.01, 4.43]
27.4.1 Normal response	1	216	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.01, 4.43]
27.5 Oocyte number	1	216	Mean Difference (IV, Random, 95% CI)	-5.08 [-7.39, -2.77]
27.5.1 Normal response	1	216	Mean Difference (IV, Random 95% CI)	-5.08 [-7.39, -2.77]
27.6 Frozen embryo number	1	216	Mean Difference (IV Random, 95% CI)	-3.09 [-4.69, -1.49]
27.6.1 Normal response	1	216	Mean Diff rence (IV, R ndom, 95% CI)	-3.09 [-4.69, -1.49]

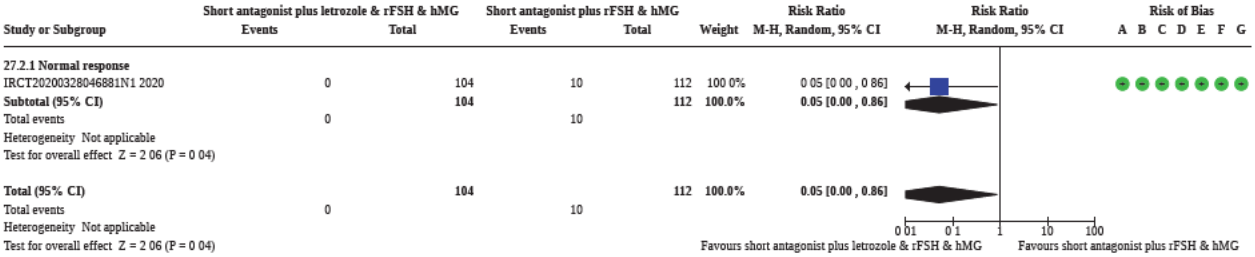
Analysis 27.1. Comparison 27: Direct comparison: Short GnRH antagonist plus letrozole, rFSH & hMG versus short GnRH antagonist plus rFSH & hMG, Outcome 1: Clinical pregnancy



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

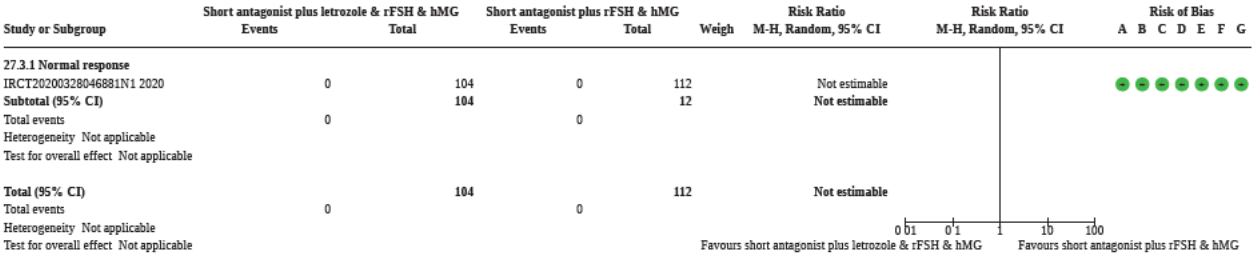
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Analysis 27.2. Comparison 27: Direct comparison: Short GnRH antagonist plus letrozole, rFSH & hMG versus short GnRH antagonist plus rFSH & hMG, Outcome 2: Miscarriage



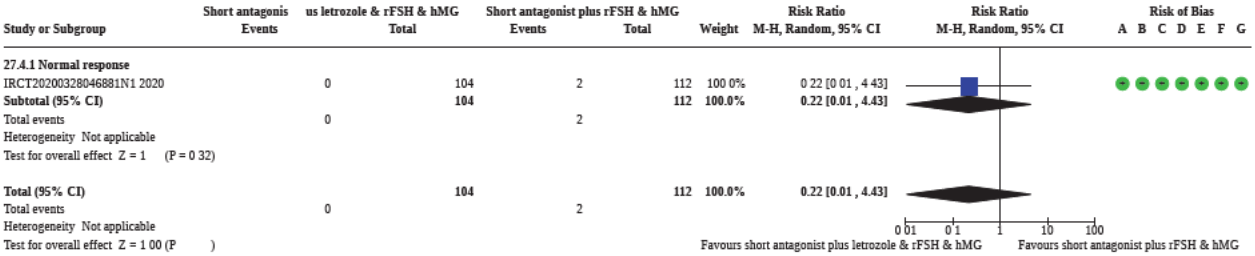
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 27.3. Comparison 27: Direct comparison: Shor GnRH antagonist plus letrozole, rFSH & hMG versus short GnRH antagonist plus rFSH & hMG, Outcome 3: Ectopic



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

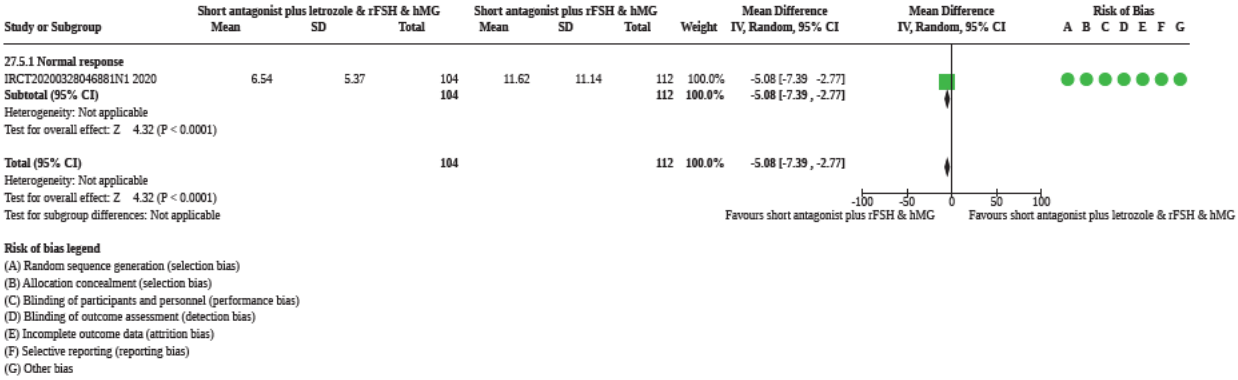
Analysis 27.4. Compar son 27: Direct comparison: Short GnRH antagonist plus letrozole, rFSH & hMG versus short GnRH antagonist plus rFSH & hMG, Outcome 4: Cancellation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

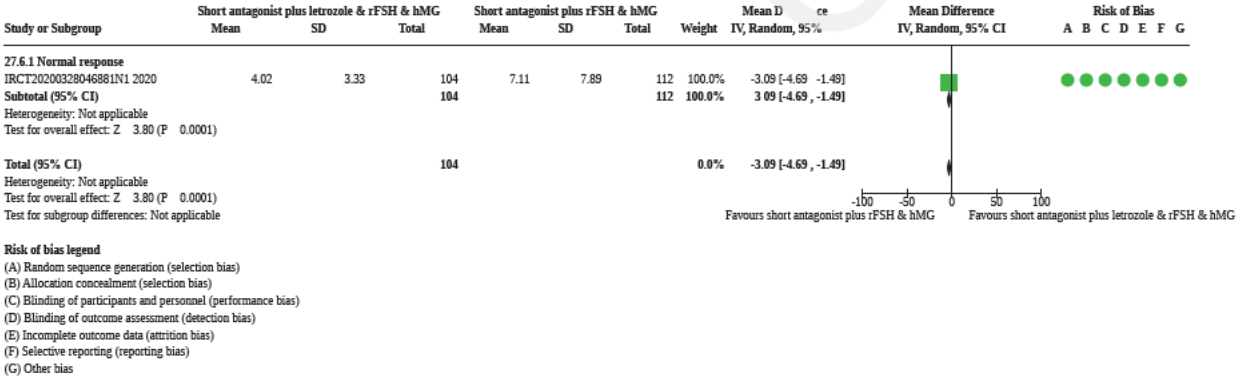
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Analysis 27.5. Comparison 27: Direct comparison: Short GnRH antagonist plus letrozole, rFSH & hMG versus short GnRH antagonist plus rFSH & hMG, Outcome 5: Oocyte number



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 27.6. Comparison 27: Direct comparison: Short GnRH ant gonist plus letrozole, rFSH & hMG versus short GnRH antagonist plus rFSH & hMG, Outcome 6 Frozen embryo number



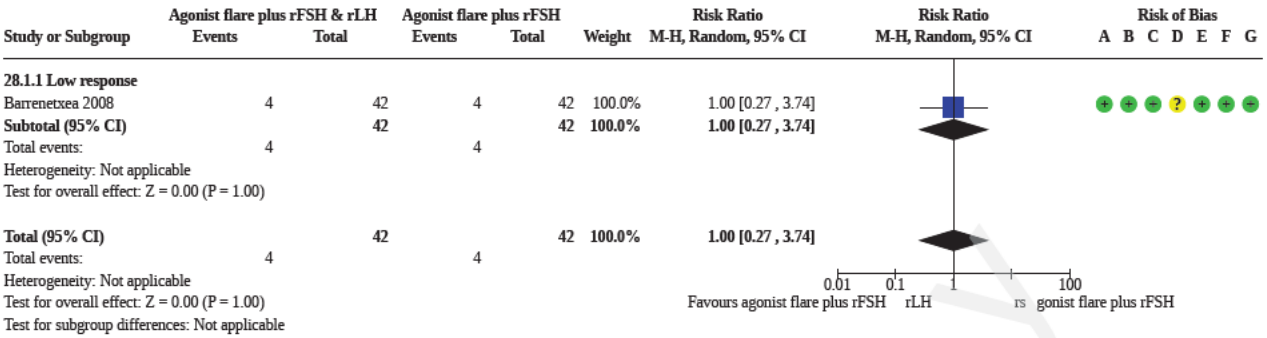
Risk of bias legend
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(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 28. Direct comparison: GnRH agonist flare plus rFSH & rLH versus GnRH agonist flare plus rFSH

Outcome or subgroup title	No. of st dies	N of partici-pants	Statistical method	Effect size
28.1 Cancellation	1	84	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.27, 3.74]
28.1.1 Low response	1	84	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.27, 3.74]
28.2 Oocyte number	1	84	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.43, -0.03]
28.2.1 Low response	1	84	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.43, -0.03]

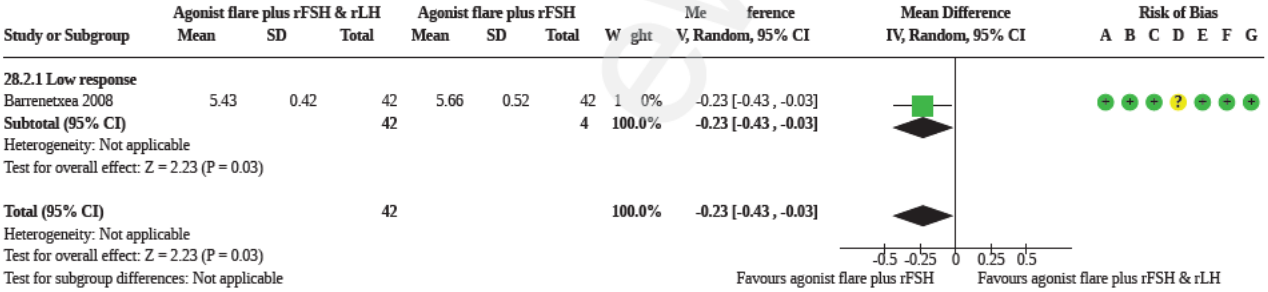
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Analysis 28.1. Comparison 28: Direct comparison: GnRH agonist flare plus rFSH & rLH versus GnRH agonist flare plus rFSH, Outcome 1: Cancellation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 28.2. Comparison 28: Direct compari on: GnRH agonist flare plus rFSH & rLH versus GnRH agonist flare plus rFSH Outcome 2: Oocyte number



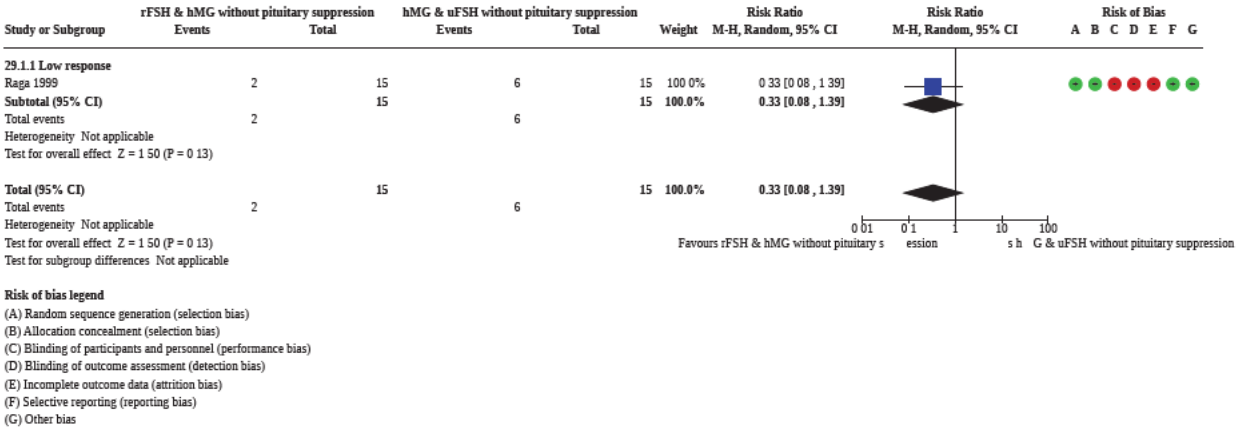
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performa e bias)
(D) Blinding of outcome assessment (detection bi
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 29. Direct comp rison: rFSH & hMG without pituitary suppression versus hMG & uFSH without pituitary suppression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29.1 Cancellation	1	30	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.39]
29.1.1 Low response	1	30	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.39]
29.2 Oocyte number	1	30	Mean Difference (IV, Random, 95% CI)	1.60 [0.17, 3.03]
29.2.1 Low response	1	30	Mean Difference (IV, Random, 95% CI)	1.60 [0.17, 3.03]

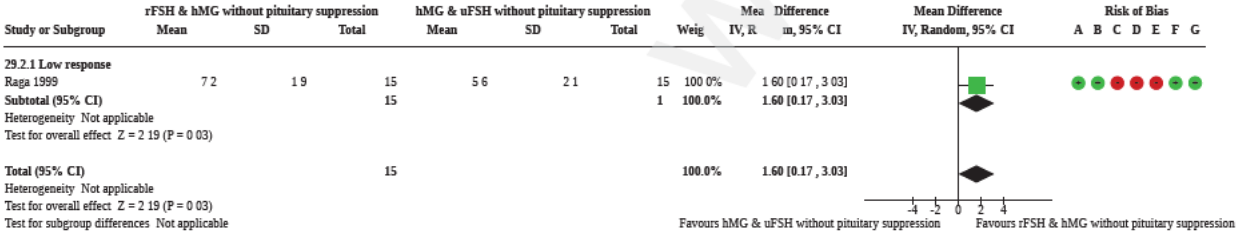
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Analysis 29.1. Comparison 29: Direct comparison: rFSH & hMG without pituitary suppression versus hMG & uFSH without pituitary suppression, Outcome 1: Cancellation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 29.2. Comparison 29: Direct comparison: rFSH & hMG without pituitary suppression versus hMG & uFSH without pituitary suppression, Outcome 2: Oocyte number



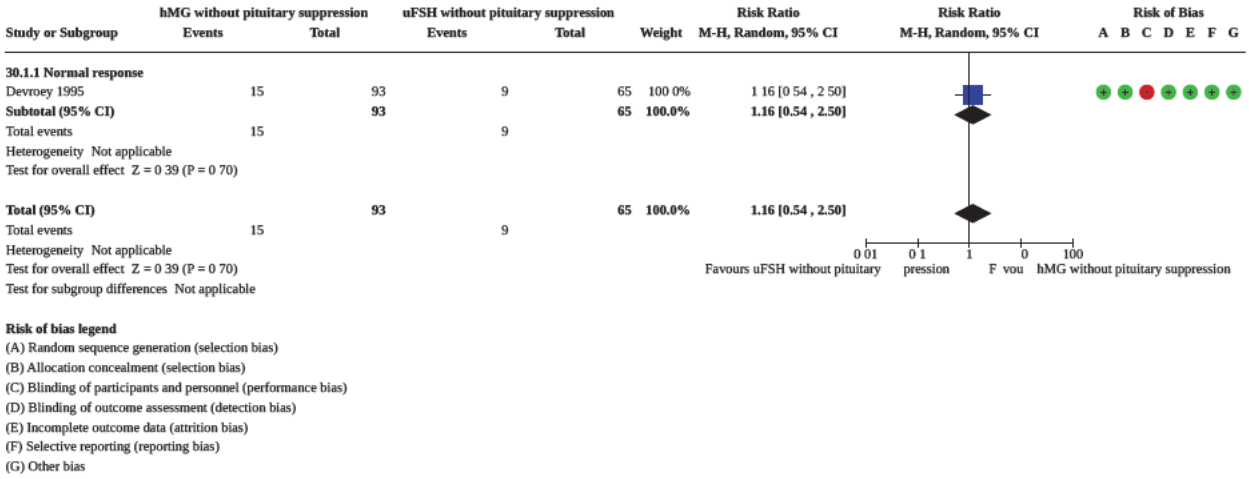
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 30. Direct comparis n: hMG without pituitary suppression versus uFSH without pituitary suppression

Outcome or subgroup title	No of studies	No. of participants	Statistical method	Effect size
30.1 Clinical pregnancy	1	158	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.54, 2.50]
30.1.1 Normal response	1	158	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.54, 2.50]
30.2 Ongoing pregnancy	1	158	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.41, 2.26]
30.2.1 Normal response	1	158	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.41, 2.26]
30.3 Cancellation	1	158	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.29, 4.70]
30.3.1 Normal response	1	158	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.29, 4.70]

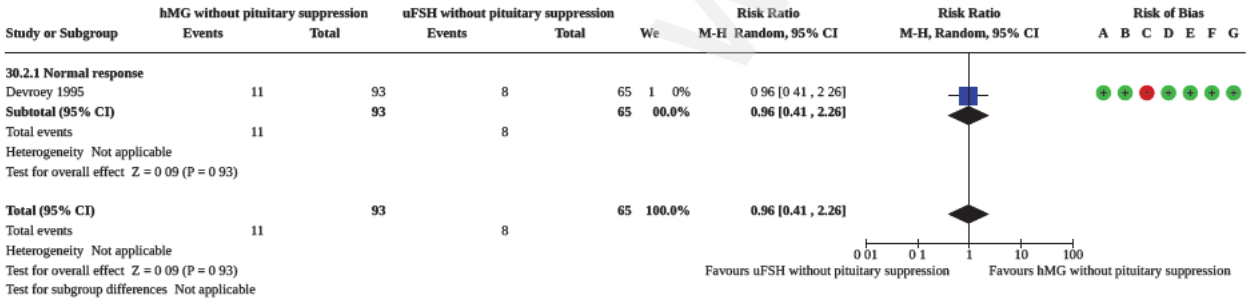
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Analysis 30.1. Comparison 30: Direct comparison: hMG without pituitary suppression versus uFSH without pituitary suppression, Outcome 1: Clinical pregnancy



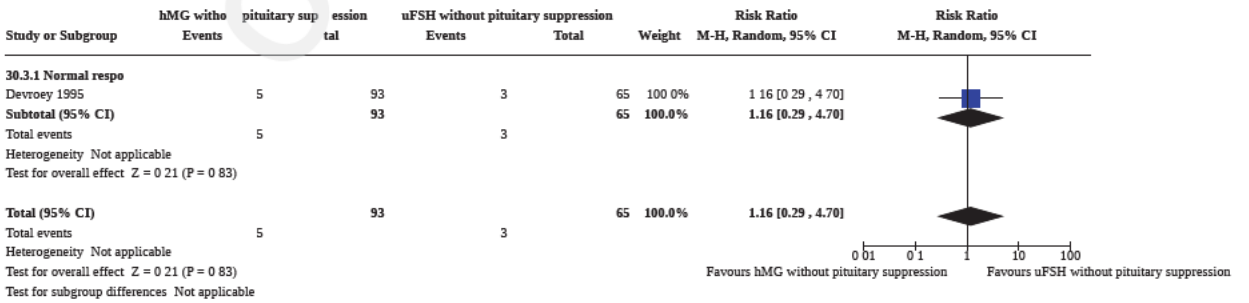
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 30.2. Comparison 30: Direct comparison: hMG without pituitary suppression versus uFSH without pituitary suppression, Ou come 2: Ongoing pregnancy



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysi 30.3. Comparison 30: Direct comparison: hMG without pituitary suppression ve sus uFSH without pituitary suppression, Outcome 3: Cancellation



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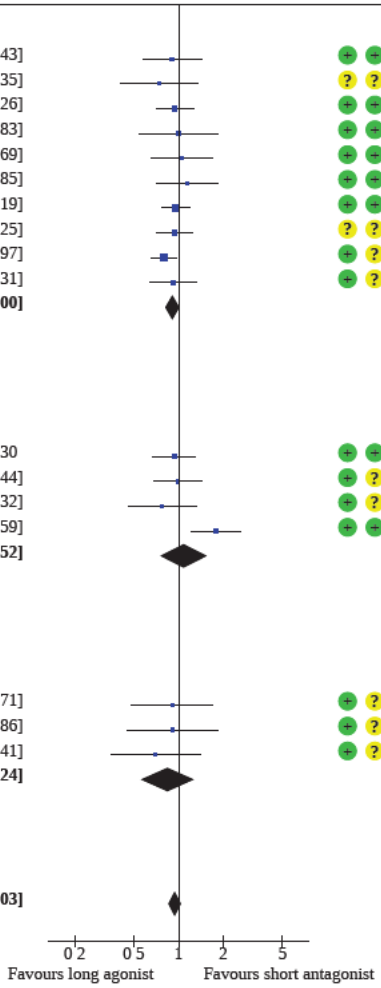
Comparison 31. Direct comparison: Sensitivity analysis - Short GnRH antagonist versus long GnRH agonist

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.1 Live birth	17	5157	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.86, 1.03]
31.1.1 Normal response	10	3624	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.00]
31.1.2 High response	4	1046	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.77, 1.52]
31.1.3 Low response	3	487	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.57, 1.24]
31.2 OHSS	31	7382	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.58, 0.87]
31.2.1 Normal response	21	5504	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.60, 1.10]
31.2.2 High response	10	1878	Risk Ratio (M H, R ndom, 95% CI)	0.61 [0.48, 0.78]

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Analysis 31.1. Comparison 31: Direct comparison: Sensitivity analysis - Short GnRH antagonist versus long GnRH agonist, Outcome 1: Live birth

Study or Subgroup	Short antagonist Events	Short antagonist Total	Long agonist Events	Long agonist Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
31.1.1 Normal response							
Albano 2000	42	188	21	85	3 7%	0 90 [0 57 , 1 43]	+ + ? ? - - +
Barmat 2005	12	39	17	41	2 2%	0 74 [0 41 , 1 35]	? ? ? ? - - +
Garcia-Velasco 2011	51	115	53	113	9 3%	0 95 [0 71 , 1 26]	+ + + + + + +
Huirne 2006	17	91	17	91	2 1%	1 00 [0 55 , 1 83]	+ - ? ? + - +
Lin 2006	22	60	21	60	3 4%	1 05 [0 65 , 1 69]	+ + + + + - +
Papanikolaou 2012	27	96	23	94	3 4%	1 15 [0 71 , 1 85]	+ + + ? + - +
Toftager 2016	122	534	123	516	15 2%	0 96 [0 77 , 1 19]	+ + - - + - +
Vlaisavljevic 2003	64	226	71	236	9 3%	0 94 [0 71 , 1 25]	? ? ? ? + - -
Xu 2020	94	273	235	546	19 7%	0 80 [0 66 , 0 97]	+ ? - - + - +
Ye 2009	37	109	41	111	6 0%	0 92 [0 64 , 1 31]	+ ? ? ? + - +
Subtotal (95% CI)		**1731**		**1893**	**74.3%**	**0.91 [0.82 , 1.00]**	
Total events:	488		622				
Heterogeneity: Tau² = 0 00; Chi² = 3 90, df = 9 (P = 0 92); I² = 0%							
Test for overall effect: Z = 1 90 (P = 0 06)							
31.1.2 High response							
Casano 2012	51	205	55	207	7 0%	0 94 [0 67 , 1 30	+ + - - + - ?
Kim 2012	36	106	36	105	5 4%	0 99 [0 68 , 1 44]	+ ? + - + - +
Kurzawa 2008	14	37	18	37	2 8%	0 78 [0 46 , 1 32]	+ ? + - + - +
Rinaldi 2014	47	148	36	201	5 3%	1 77 [1 21 , 2 59]	+ + + - - - ?
Subtotal (95% CI)		**496**		**550**	**20.6%**	**1.08 [0.77 , 52]**	
Total events:	148		145				
Heterogeneity: Tau² = 0 08; Chi² = 9 01, df = 3 (P = 0 03); I² = 67%							
Test for overall effect: Z = 0 44 (P = 0 66)							
31.1.3 Low response							
Kim 2011	20	80	11	40	2 0%	0 [0 8 , 1 71]	+ ? ? ? + - ?
Liu 2020	13	101	14	100	1 6%	92 [0 6 , 1 86]	+ ? - - - - +
Yu 2018	16	112	11	54	1 6%	70 0 35 , 1 41]	+ ? ? ? - - +
Subtotal (95% CI)		**293**		**194**	**5.1%**	**0.84 [0.57 , 1.24]**	
Total events:	49		36				
Heterogeneity: Tau² = 0 00; Chi² = 0 38, df = 2 (P = 0 83); I² = 0%							
Test for overall effect: Z = 0 87 (P = 0 38)							
Total (95% CI)		**2520**		**2 37**	**1 0.0**	**0.94 [0.86 , 1.03]**	
Total events:	685		803				
Heterogeneity: Tau² = 0 00; Chi² = 16 44, df = 16 (P = 0 42); = 3%							
Test for overall effect: Z = 1 35 (P = 0 18)							
Test for subgroup differences: Chi² = 1 11, df = 2 = 0 7), I² = %							

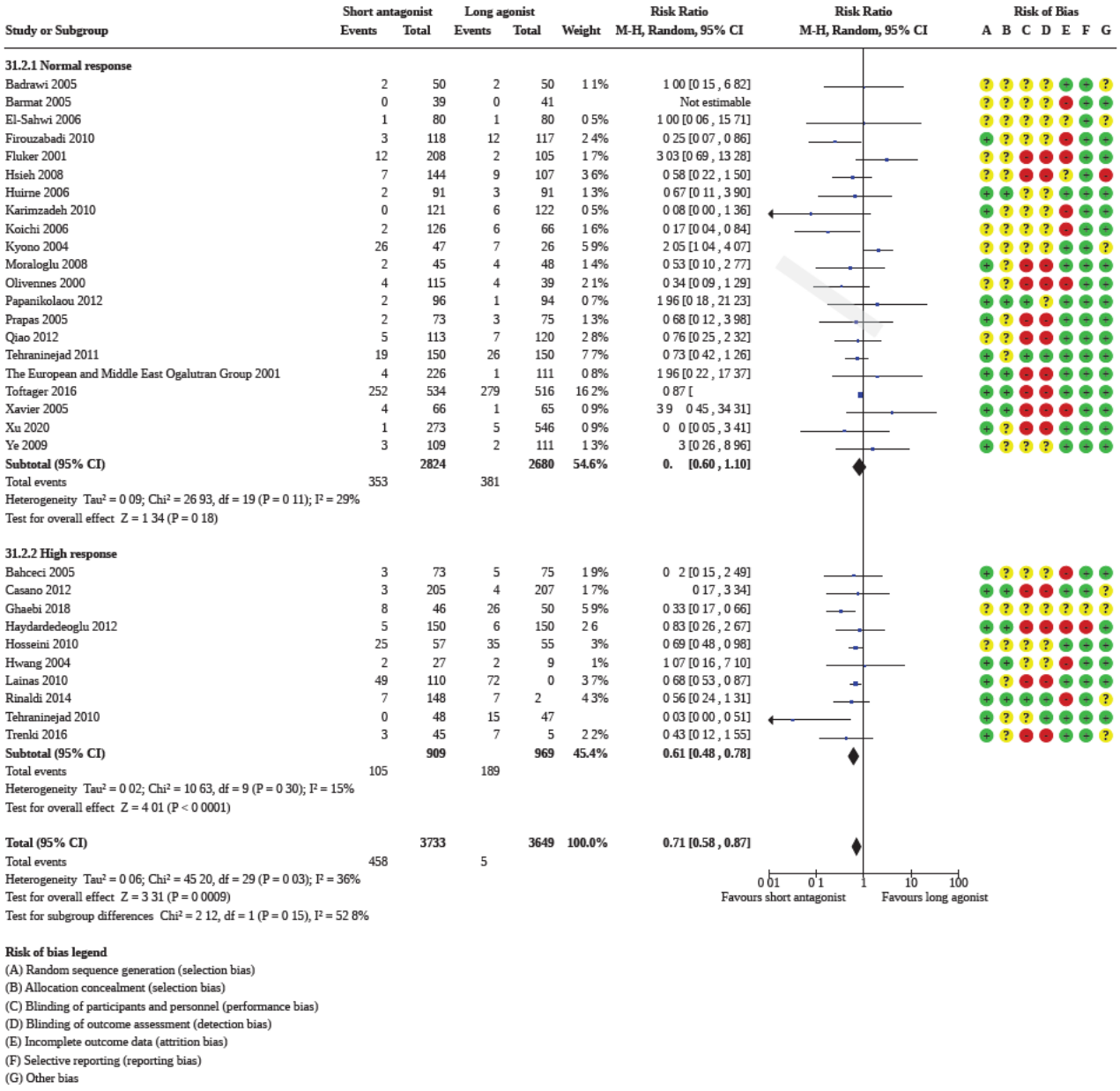


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bi s)
(D) Blinding of outcome assessment (det tion bias)
(E) Incomplete outcome data (attrition b)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 31.2. Comparison 31: Direct comparison: Sensitivity analysis - Short GnRH antagonist versus long GnRH agonist, Outcome 2: OHSS



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

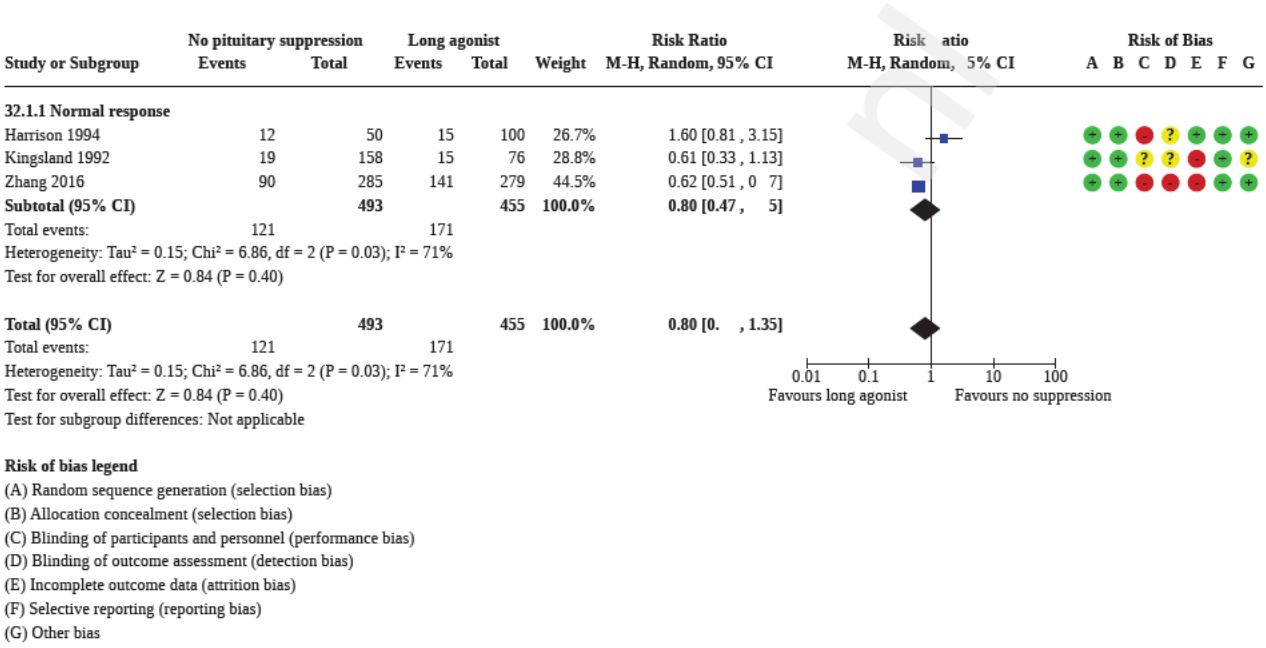
Comparison 32. Direct ompar son: Sensitivity analysis - No pituitary suppression versus long GnRH agonist protocols

Outcome or subgro p title	No. of studies	No. of partici-pants	Statistical method	Effect size
32.1 Live birth	3	948	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.47, 1.35]
32.1.1 Normal response	3	948	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.47, 1.35]
32.2 OHSS	2	408	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.10, 0.78]

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
32.2.1 Normal response	1	294	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.10, 0.92]
32.2.2 High response	1	114	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.70]

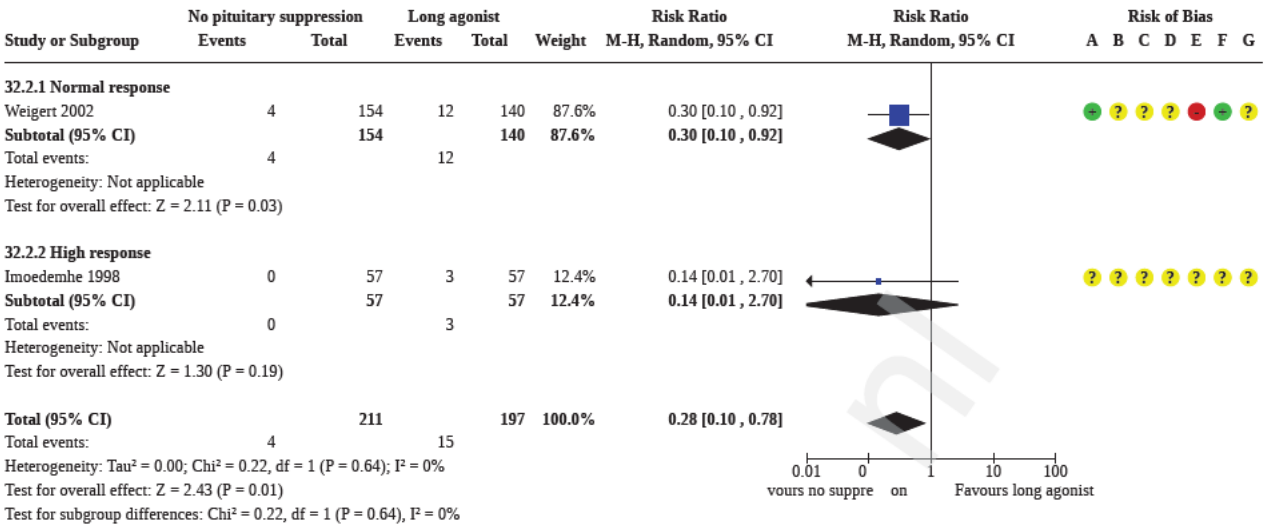
Analysis 32.1. Comparison 32: Direct comparison: Sensitivity analysis - No pituitary suppression versus long GnRH agonist protocols, Outcome 1: L ve birth



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 32.2. Comparison 32: Direct comparison: Sensitivity analysis - No pituitary suppression versus long GnRH agonist protocols, Outcome 2: OHSS



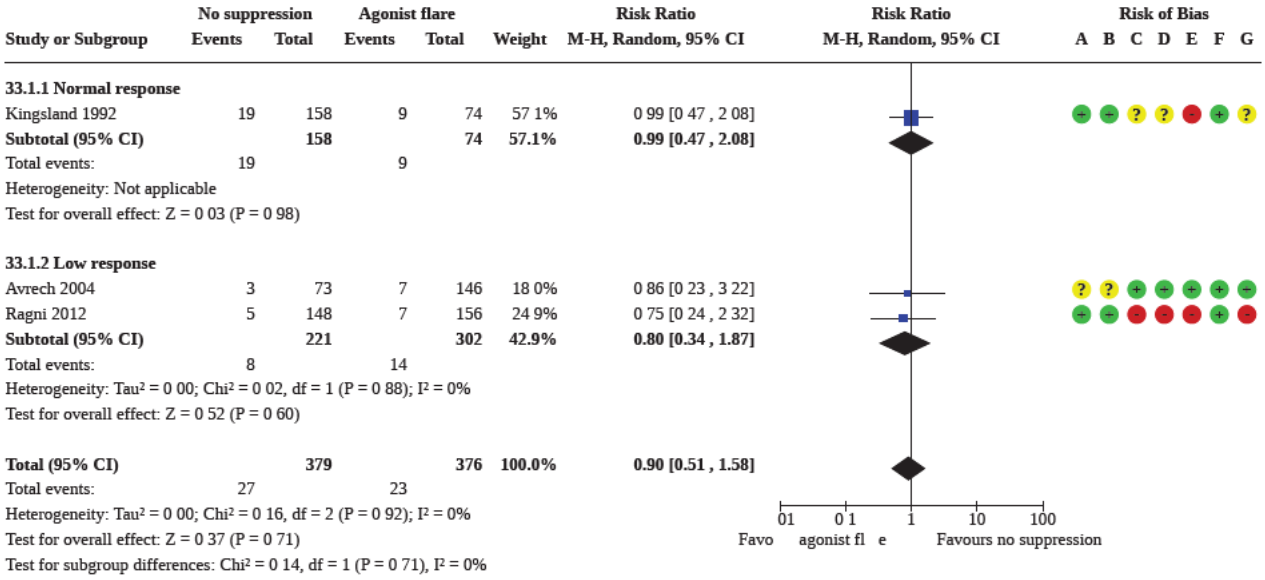
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 33. Direct comparison: Sensitivity analysis No pituitary suppression versus GnRH agonist flare protocols

Outcome or subgroup title	No. of studies	No of participants	Statistical method	Effect size
33.1 Live birth	3	755	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.51, 1.58]
33.1.1 Normal response	1	232	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.47, 2.08]
33.1.2 Low response	2	523	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.34, 1.87]

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Analysis 33.1. Comparison 33: Direct comparison: Sensitivity analysis - No pituitary suppression versus GnRH agonist flare protocols, Outcome 1: Live birth



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

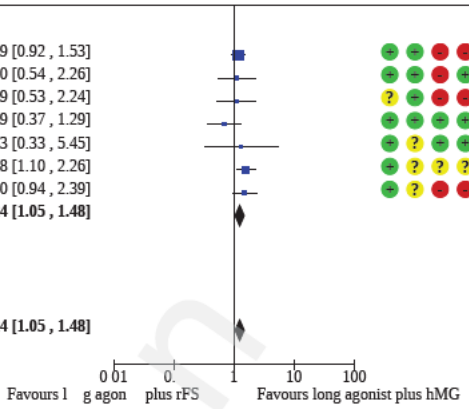
Comparison 34. Direct comparison: Sensitivity an lysis - Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH

Outcome or subgroup title	No. of studies	N of pa tici-pants	Statistical method	Effect size
34.1 Live birth	7	1575	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.05, 1.48]
34.1.1 Normal response	7	1575	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.05, 1.48]
34.2 OHSS	7	3091	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.49, 1.52]
34.2.1 Normal response	6	3007	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.60, 1.62]
34.2.2 High response	1	84	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.59]

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Analysis 34.1. Comparison 34: Direct comparison: Sensitivity analysis - Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH, Outcome 1: Live birth

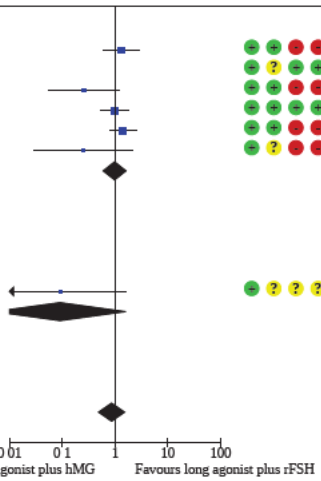
Study or Subgroup	Long agonist plus hMG Events	Total	Long agonist plus rFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
34.1.1 Normal response						
Andersen 2006	96	363	82	368	43.8%	1.19 [0.92 , 1.53]
Gordon 2001	15	59	9	39	5.7%	1.10 [0.54 , 2.26]
Kilani 2003	12	50	11	50	5.7%	1.09 [0.53 , 2.24]
Parsanezhad 2017	11	40	16	40	7.4%	0.69 [0.37 , 1.29]
Rashidi 2005	4	30	3	30	1.5%	1.33 [0.33 , 5.45]
Westergaard 2001	58	189	37	190	22.5%	1.58 [1.10 , 2.26]
Ye 2012	28	63	19	64	13.4%	1.50 [0.94 , 2.39]
Subtotal (95% CI)		**794**		**781**	**100.0%**	**1.24 [1.05 , 1.48]**
Total events:	224		177			
Heterogeneity: Tau² = 0.00; Chi² = 6.04, df = 6 (P = 0.42); I² = 1%						
Test for overall effect: Z = 2.49 (P = 0.01)						
Total (95% CI)		**794**		**781**	**100.0%**	**1.24 [1.05 , 1.48]**
Total events:	224		177			
Heterogeneity: Tau² = 0.00; Chi² = 6.04, df = 6 (P = 0.42); I² = 1%						
Test for overall effect: Z = 2.49 (P = 0.01)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 34.2. Comparison 34: Direc comp rison: Sensitivity analysis - Long GnRH agonist plus hMG versus long GnRH agonist plus rFSH, Outcome 2: OHSS

Study or Subgroup	Long agonist plus hMG Events	Total	Long agonist p rFSH Eve al	Weight	Risk Ratio M-H, Random, 95% CI
34.2.1 Normal response					
Andersen 2006	13	363	10 368	22 7%	1 32 [0 59 , 2 97]
Balasch 2003	0	3	0 30		Not estimable
Hompes 2008	2	312	317	10 3%	0 25 [0 05 , 1 19]
Melo 2010	19	333	0 346	28 4%	0 99 [0 54 , 1 82]
The European and Israeli Study Group 2002	26	395	18 386	29 2%	1 41 [0 79 , 2 53]
Ye 2012		3	4 64	5 9%	0 25 [0 03 , 2 21]
Subtotal (95% CI)		**1496**	**1511**	**96.4%**	**0.98 [0.60 , 1.62]**
Total events	61		60		
Heterogeneity Tau² = 0 11; Chi² = 6 28, df = 4 (P = 0 1 ² = 36%					
Test for overall effect Z = 0 07 (P = 0 95)					
34.2.2 High response					
Turkcapar 2013	0	42	5 42	3 6%	0 09 [0 01 , 1 59]
Subtotal (95% CI)		**42**	**42**	**3.6%**	**0.09 [0.01 , 1.59]**
Total events	0		5		
Heterogeneity Not applicable					
Test for overall effect Z = 1 64 (P = 0 10)					
Total (95% CI)		**1538**	**1553**	**100.0%**	**0.86 [0.49 , 1.52]**
Total events	61		65		
Heterogeneity Tau² = 0 Chi² = 9 24, df P 10); I² = 46%					
Test for overall effect 0 51 (P 61)					
Test for subgroup di nces Ch 2 58, df = 1 (P = 0 11), I² = 61 2%					





Risk of bias legend
(A) Random sequence generation (s t on bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

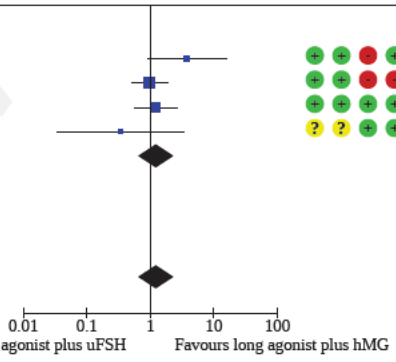
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Comparison 35. Direct comparison: Sensitivity analysis - Long GnRH agonist plus hMG versus long GnRH agonist plus uFSH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
35.1 Live birth	4	322	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.67, 2.22]
35.1.1 Normal response	4	322	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.67, 2.22]
35.2 OHSS	1	25	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.57, 1.35]
35.2.1 High response	1	25	Risk Ratio (M-H, Random 95%)	0.87 [0.57, 1.35]

Analysis 35.1. Comparison 35: Direct comparison: S itivity analysis - Long GnRH agonist plus hMG versus long GnRH agonist pl s uFSH, utcome 1: Live birth

Study or Subgroup	Long agonist hMG Events	Total	Long agonist uFSH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
35.1.1 Normal response						
Gordon 2001	15	59	2	30	15.0%	3.81 [0.93 , 60]
Miron 1998	13	54	14	57	42.6%	0.98 51 , 1.89]
Parsanezhad 2017	11	40	9	40	36.1%	1.22 [0 57 , 2.
Yang 1995	1	25	2	17	6.2%	34 [0.03 3.46]
Subtotal (95% CI)		**178**		**144**	**100.0%**	**1.22 [0.6 22]**
Total events:	40		27			
Heterogeneity: Tau² = 0.11; Chi² = 4.20, df = 3 (P = 0.24); I² = 29%						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**178**		**144**	**100 %**	**1.22 [0.67 , 2.22]**
Total events:	40		27			
Heterogeneity: Tau² = 0.11; Chi² = 4.20, df = 3 (P = 0.24); I² = 29%						
Test for overall effect: Z = 0.65 (P = 0.52)						
Test for subgroup differences: Not applicable						





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (perform nce s)
(D) Blinding of outcome assessment (detection b s)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Analysis 35.2. Comparison 35: Direct comparison: Sensitivity analysis - Long GnRH agonist plus hMG versus long GnRH agonist plus uFSH, Outcome 2: OHSS



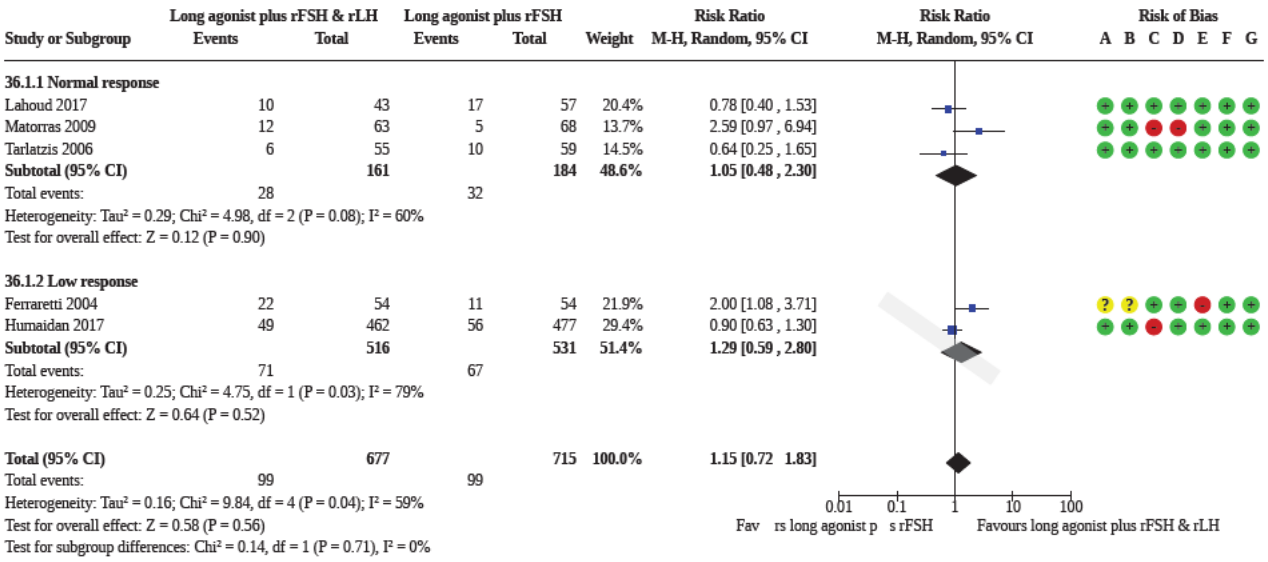
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 36. Direct comparison: Sensitivity analysis - Long G RH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH

Outcome or subgroup title	No. of studies	No. of partici-pants	Stat stical method	Effect size
36.1 Live birth	5	1392	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.72, 1.83]
36.1.1 Normal response	3	345	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.48, 2.30]
36.1.2 Low response	2	10 7	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.59, 2.80]
36.2 OHSS	4	420	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.03, 0.90]
36.2.1 Normal response	4	1420	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.03, 0.90]

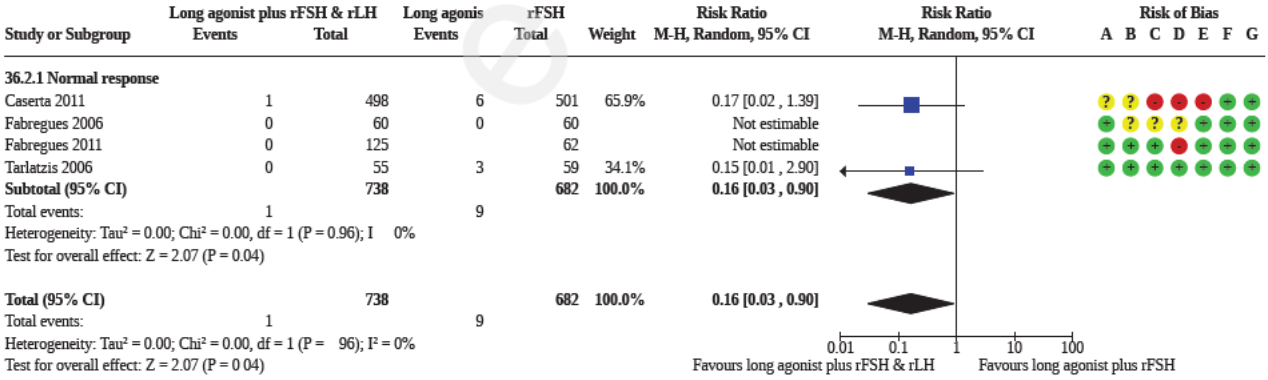
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Analysis 36.1. Comparison 36: Direct comparison: Sensitivity analysis - Long GnRH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH, Outcome 1: Live birth



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 36.2. Comparison 36: Direct comparison: Sensitivity analysis - Long GnRH agonist plus rFSH & rLH versus long GnRH agonist plus rFSH, Outcome 2: OHSS



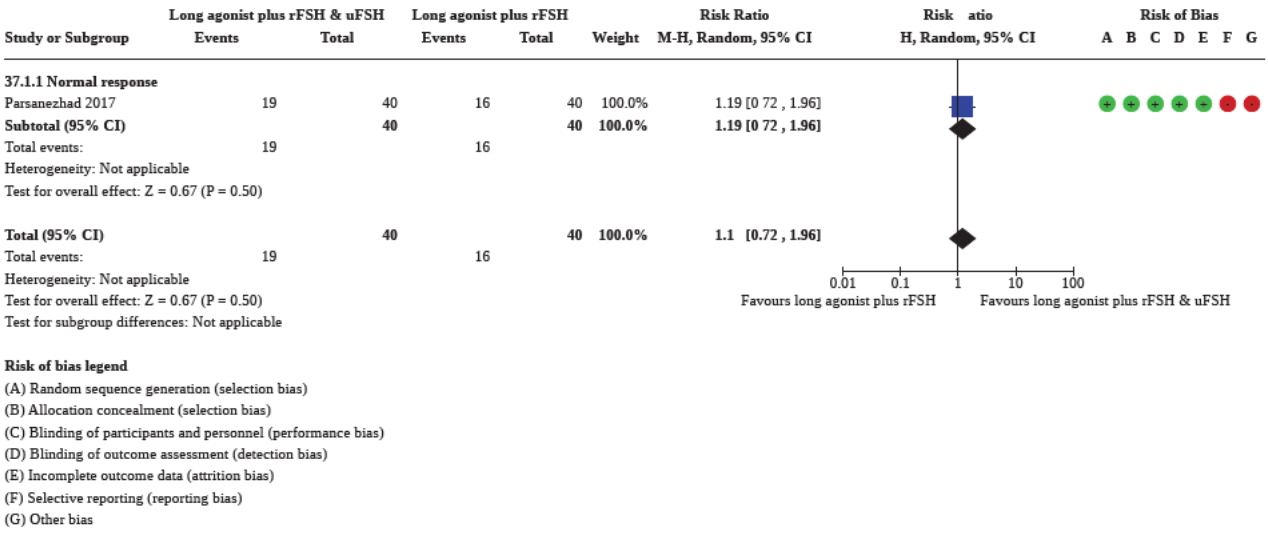
Risk of bias legend
(A) Random sequen generatio (selection bias)
(B) Allocation conc ment (ection bias)
(C) Blinding of participan nd personnel (performance bias)
(D) Blinding of outcome asses nt (detection bias)
(E) Incomplete outcome data (attrit on bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Comparison 37. Direct comparison: Sensitivity analysis - Long GnRH agonist plus rFSH or uFSH versus long GnRH agonist plus rFSH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37.1 Live birth	1	80	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.72, 1.96]
37.1.1 Normal response	1	80	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.72, 1.96]

Analysis 37.1. Comparison 37: Direct comparison: Sensitivity analysis - Long GnRH agonist plus rFSH or uFSH versus long GnRH agonist plus rFSH, Outcome 1: Live birth



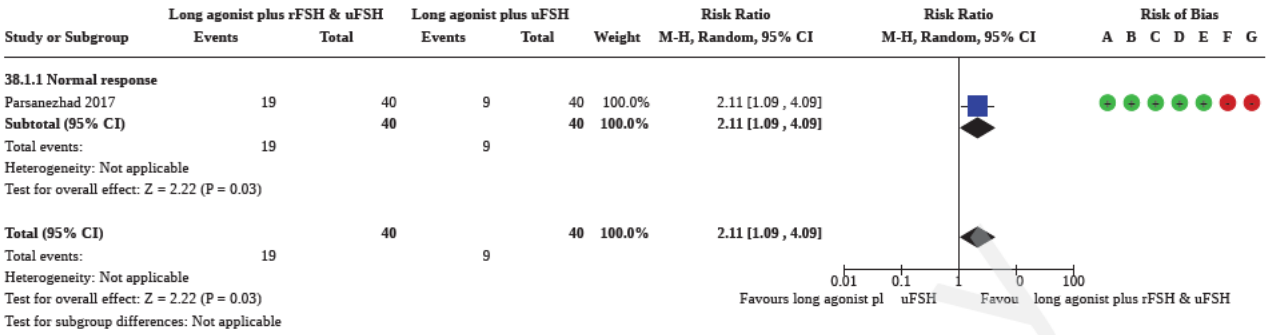
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 38. Direct comparison: Sens tivity nalysis - Long GnRH agonist plus rFSH or uFSH versus long GnRH agonist plus uFSH

Outcome or subgroup title	No. of tudies	No. of participants	Statistical method	Effect size
38.1 Live birth	1	80	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.09, 4.09]
38.1.1 Normal response	1	80	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.09, 4.09]
38.2 OHSS	1	46	Risk Ratio (M-H, Random, 95% CI)	Not estimable
38.2.1 Normal response	1	46	Risk Ratio (M-H, Random, 95% CI)	Not estimable

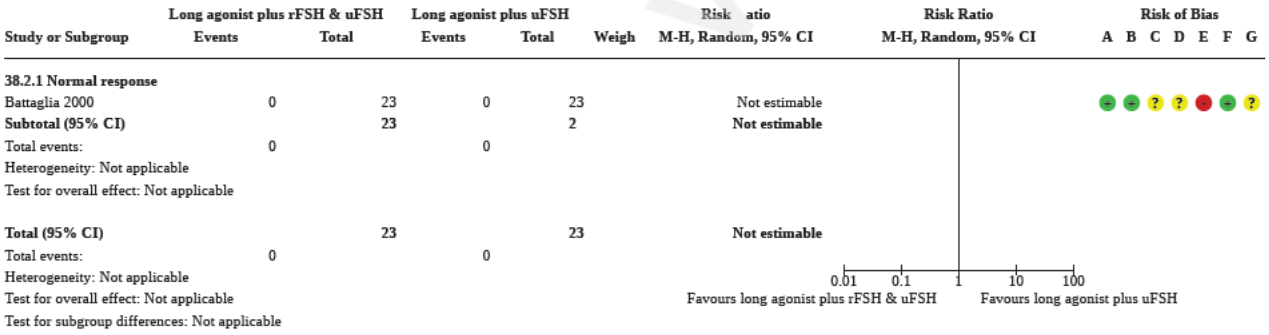
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Analysis 38.1. Comparison 38: Direct comparison: Sensitivity analysis - Long GnRH agonist plus rFSH or uFSH versus long GnRH agonist plus uFSH, Outcome 1: Live birth



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 38.2. Comparison 38: Direct comparison: Sensitivity analysis - Long GnRH agonist plus rFSH or uFSH versus long GnRH a nis plus uFSH, Outcome 2: OHSS



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performa bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

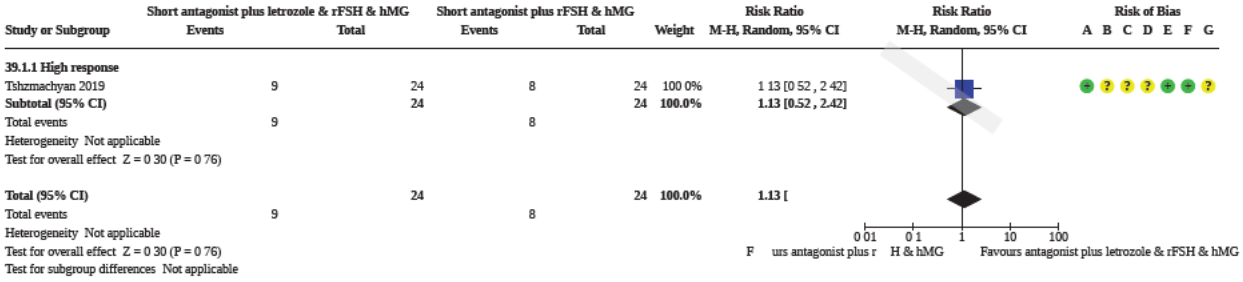
Comparison 39. Direct ompar son: Sensitivity analysis - Short GnRH antagonist plus letrozole & hMG & rFSH versus short GnRH anta onist pl s rFSH & hMG

Outcome or subg up title	No. of studies	No. of partici-pants	Statistical method	Effect size
39.1 Live birth	1	48	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.52, 2.42]
39.1.1 High response	1	48	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.52, 2.42]
39.2 OHSS	1	48	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.05, 0.92]

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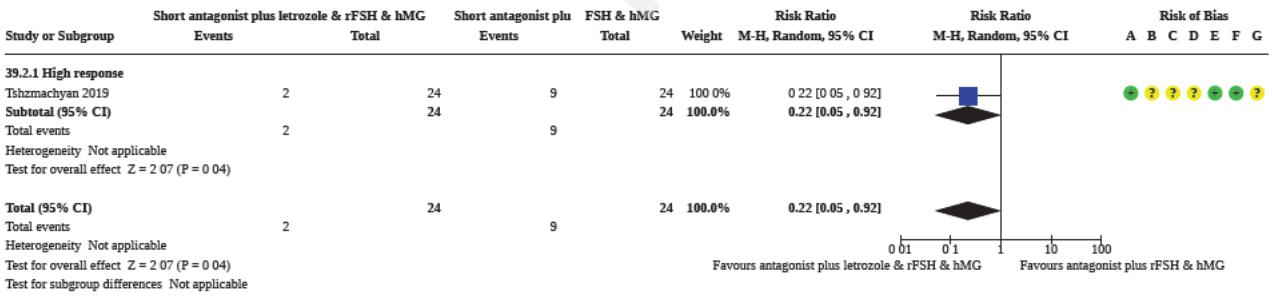
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
39.2.1 High response	1	48	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.05, 0.92]

Analysis 39.1. Comparison 39: Direct comparison: Sensitivity analysis - Short GnRH antagonist plus letrozole & hMG & rFSH versus short GnRH antagonist plus rFSH & hMG, Outcome 1: Live birth



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 39.2. Comparison 39: Direct compar son: S nsitivity analysis - Short GnRH antagonist plus letrozole & hMG & rFSH versus short G RH a tagonist plus rFSH & hMG, Outcome 2: OHSS



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (perform bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

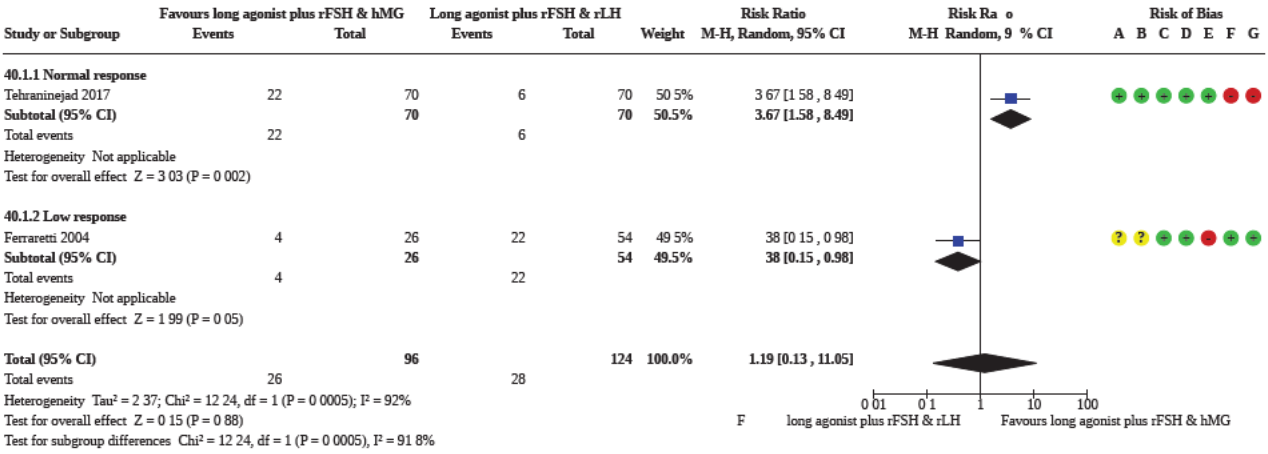
Comparison 40. Di ect comparison: Sensitivity analysis - Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus rFSH & r H

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40.1 Live birth	2	220	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.13, 11.05]
40.1.1 Normal response	1	140	Risk Ratio (M-H, Random, 95% CI)	3.67 [1.58, 8.49]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40.1.2 Low response	1	80	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.15, 0.98]

Analysis 40.1. Comparison 40: Direct comparison: Sensitivity analysis - Long GnRH agonist plus rFSH & hMG versus long GnRH agonist plus rFSH & rLH, Outcome 1: Live birth



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

APPENDICES

Appendix 1. Cochrane Gynaecology a d Fer ility Group specialised register search strategy

From inception until present

Procite platform

Keywords CONTAINS "IVF" or "ICS " or "ET" or "intracytoplasmic sperm injection techniques" or "intracytoplasmic sperm injection" or "in-vitro fertilisation " or "in itro fertilization" or "Embryo Transfer" or "ovarian stimulation" or "ovarian stimulation controlled ovarian stimulation" or "ovulation induction" or "ovulation stimulation" or "superovulation" or "superovulation induction" or "ovarian hyperstimulation" or "poor espo ders or "poor responder" or "poor prognostic patients" or "controlled ovarian hyperstimulation" or "controlled ovarian stimula ion" or COH" or Title CONTAINS "IVF" or "ICSI" or "ET" or "intracytoplasmic sperm injection techniques" or "intracytoplasmi sperm i jection" or "in-vitro fertilisation " or "in vitro fertilization" or "Embryo Transfer" or "ovarian stimulation" or "ovarian stimu ation ontrolled ovarian stimulation" or "ovulation induction" or "ovulation stimulation" or "superovulation" or "superovulation induct on" or "ovarian hyperstimulation" **AND** Keywords CONTAINS "long agonist protocol" or "long-long protocol" or "long protocol" or ong v short protocol" or "short protocol" or "stimulated cycle" or "Stimulation techniques" or "stop protocol" or "flare-down" or "flare-up" or "flare-up GnRH agonist" or "flare-up protocol" or "micro-dose GnRH-a flare" or "micro-dose HCG" or "microdose flare cycle" or "microdose flare-up protocol" or "microdose GnRH agonist flare" or "microg IN buserelin" or "flexible protocol" or "multidose antagonist protocol" or "GnRH agonist short protocol" or "GnRH agonist vs antagonist" or "gonadotrophin stimulation" or "Gonal-F" or "mild ovarian stimulation" or "mild protocol" or "mild stimulated" or "mild stimulation" or "Gonal-F" or "GnRH a" or "GnRH agonist" or "GnRH agonists" or "GnRH analog" or "GnRH analogue" or "GnRH analogues" or "GnRH antagonist" or "GnRH antagonists" or "GnRHa" or "GnRHa-gonadotropin" or "Gonadorelin" or "gonadotropin releasing hormone agonist" or "Gonadotrophin releasing agonist" or "natural cycle" or "natural cycles" or "modified natural cycle" or "artificial cycle"

OR

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Keywords CONTAINS "IVF" or "ICSI" or "ET" or "intracytoplasmic sperm injection techniques" or "intracytoplasmic sperm injection" or "in-vitro fertilisation " or "in vitro fertilization" or "Embryo Transfer" or "ovarian stimulation" or "ovarian stimulation controlled ovarian stimulation" or "ovulation induction" or "ovulation stimulation" or "superovulation" or "superovulation induction" or "ovarian hyperstimulation" or "poor responders" or "poor responder" or "poor prognostic patients" or "controlled ovarian hyperstimulation" or "controlled ovarian stimulation" or "COH" or Title CONTAINS "IVF" or "ICSI" or "ET" or "intracytoplasmic sperm injection techniques" or "intracytoplasmic sperm injection" or "in-vitro fertilisation " or "in vitro fertilization" or "Embryo Transfer" or "ovarian stimulation" or "ovarian stimulation controlled ovarian stimulation" or "ovulation induction" or "ovulation stimulation" or "superovulation" or "superovulation induction" or "ovarian hyperstimulation" **AND** Keywords CONTAINS "standard IVF-ICSI procedure" or "standard protocol "or "standard schedule" or "standard stimulation" or "individualised protocol" or "individualized protocol" or "multiple dose protocol" or "Pretreatment" or "mini-IVF" or "minidose GnRH agonist" or "minidose long GnRH agonist" or "minimal stimulation" or "micro-dose GnRH-a flare" or "minidose" or "flexible protocol" or "co-flare protocol" or "Pretreatment" or "GNRH antagonist protocol" or ultra long protocol" or "ultra low-dose" or "ultra-short protocol" or "down regulation" or "fixed dose protocol" or "fixed protocol" or "protocol" or "Protocols" or "multiple dose" or "multiple dose" or "LHRH" or "LHRH agonists" or "LHRH antagonists"

Appendix 2. CENTRAL search strategy

From inception until present

Central Register of Studies Online (CRSO) web platform

#1 MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES

#2 (embryo transfer*):TI,AB,KY

#3 (vitro fertili?ation*):TI,AB,KY

#4 (ivf or ICSI):TI,AB,KY

#5 (intracytoplasmic sperm injection*):TI,AB,KY

#6 (blastocyst transfer*):TI,AB,KY

#7 (assisted reproduct*):TI,AB,KY

#8 superovulat*:TI,AB,KY

#9 COH:TI,AB,KY

#10 MESH DESCRIPTOR Ovulation Induction EXPLODE AL TREES

#11 (ovar* adj3 stimulat*):TI,AB,KY

#12 (ovar* adj3 hyperstimulat*):TI,AB,KY

#13 (ovar* adj3 induc*):TI,AB,KY

#14 (ovulat* adj3 induc*):TI,AB,KY

#15 (ovul* adj3 stimulat*):TI,AB,KY

#16 (oocyte* adj2 matur*):TI,AB,KY

#17 folliculogenesis:TI,AB,KY

#18 (ovar* adj2 ster idogenes s):TI AB,KY

#19 (poor adj2 resp n*) TI,AB,KY

#20 (poor prognos*):TI,AB,KY

#21 (low adj2 respon*):TI,AB,KY

#22 (recurrent adj2 failure*):TI,AB,KY

#23 (poor adj2 reserve):TI,AB,KY

#24 (infertil* or subfertil*):TI,AB,KY

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#25 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

#26 MESH DESCRIPTOR Menotropins EXPLODE ALL TREES

#27 (human menopausal gonadotrop?in*):TI,AB,KY

#28 pergonal:TI,AB,KY

#29 Menotrop?in*:TI,AB,KY

#30 (hMG or hphMG):TI,AB,KY

#31 menopur:TI,AB,KY

#32 Merional-HG:TI,AB,KY

#33 hume?gon:TI,AB,KY

#34 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33

#35 MESH DESCRIPTOR Follicle Stimulating Hormone, Human EXPLODE ALL TREES

#36 (recombinant follicle stimulating hormone*):TI,AB,KY

#37 (recombinant FSH):TI,AB,KY

#38 (rec FSH or rFSH or rhFSH or hFSH):TI,AB,KY

#39 (recFSH or Gonal F):TI,AB,KY

#40 (Human FSH or Fostimon):TI,AB,KY

#41 (pFSH or p-FSH or hpFSH or hp-FSH):TI,AB,KY

#42 Bemfola:TI,AB,KY

#43 r-hFSH:TI,AB,KY

#44 (FSH HP):TI,AB,KY

#45 (purified Follicle Stimulating Hormone*):TI,AB,KY

#46 (urinary adj2 follicle stimulating hormone): AB,KY

#47 (uFSH or urinary FSH or u-FSH):TI AB,KY

#48 (long acting adj3 FSH):TI,AB,KY

#49 (long acting adj2 follicle stimulating hormone):TI,AB,KY

#50 (daily FSH):TI,AB,KY

#51 (corifollitropin alpha or corifoll ropin alfa):TI,AB,KY

#52 Elonva:TI,AB,KY

#53 (follitropin be or f llitropin alpha or follitropin alfa):TI,AB,KY

#54 Ovaleap:TI,AB,KY

#55 (recombinant adj2 gonadotrop?in*):TI,AB,KY

#56 (urinary adj2 gonadotrop?in*):TI,AB,KY

#57 (purified adj2 gonadotrop?in*):TI,AB,KY

#58 (rFSH LH):TI,AB,KY

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#59 (recombinant LH or recombinant luteinizing hormone*):TI,AB,KY

#60 (rec LH or recLH):TI,AB,KY

#61 (growth hormone):TI,AB,KY

#62 HPuFSH:TI,AB,KY

#63 (purified adj2 FSH):TI,AB,KY

#64 (exogenous gonadotrop?in*):TI,AB,KY

#65 #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR 48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64

#66 #34 OR #65

#67 (mild adj2 stimulation):TI,AB,KY

#68 (mild adj2 ivf):TI,AB,KY

#69 (microflare or flare):TI,AB,KY

#70 (agonist adj2 stop):TI,AB,KY

#71 (GNRHa or GNRH a or GNRH agonist*):TI,AB,KY

#72 (gonadotrop?in* adj3 agonist*):TI,AB,KY

#73 (GNRH antagonist* or gonadotrop?in antagonist*):TI,AB,KY

#74 MESH DESCRIPTOR Gonadotropin-Releasing Hormone EXPLODE ALL TREES

#75 (buserelin or goserelin or leuprolide or nafarelin or triptorelin) TI AB,KY

#76 (Zoladex or ganirelix or cetrorelix):TI,AB,KY

#77 (degarelix or elagolix):TI,AB,KY

#78 (factrel or down regulation):TI,AB,KY

#79 (cetrotide or lupron or synarel):TI,AB,KY

#80 (GNRH analog* or gonadotrop?in analog*):T AB,KY

#81 #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80

#82 (modified adj3 cycle*):TI,AB,KY

#83 (natural adj3 cycle*):TI,AB,KY

#84 (MNC IVF or NCIVF):TI,AB,KY

#85 (NC IVF):TI,AB,KY

#86 (unstimulated a j2 cycle TI AB,KY

#87 (unstimulated dj3 vf):TI,AB,KY

#88 (unstimulated adj2 in itro fertili?ation):TI,AB,KY

#89 (artificial adj3 cycle*):TI,AB,KY

#90 (mini* adj2 ivf):TI,AB,KY

#91 #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90

#92 #66 or #81 or #91

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#93 protocol* adj2 (mild or minimal or short or long or flare or stop or microflare) #94 protocol* adj2 (ultrashort or ultra short)

#95 protocol* adj2 (ivf or rescue or multidose or modified or flexible)

#96 protocol* adj2 (stimulat* or unstimulat*)

#97 protocol* adj2 (agonist* or antagonist*)

#98 protocol* adj2 (hyperstimulation or suppress*)

#99 protocol* adj2 (standard or gonadotrop?in*)

#100 protocol* adj2 (conventional or combined)

#101 (protocol* adj2 assisted reproduct* techn*)

#102 #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101

#103 #92 OR #102

#104 #25 AND #103

Appendix 3. MEDLINE search strategy

From 1946 to present

Ovid platform

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections intracytoplasmic/
2 embryo transfer$.tw.
3 vitro fertili?ation.tw.
4 ivf.tw.
5 icsi.tw.
6 intracytoplasmic sperm injection$.tw.
7 (blastocyst adj2 transfer$).tw.
8 assisted reproduct$.tw.
9 superovulat$.tw.
10 COH.tw.
11 exp Ovulation Induction/
12 exp Superovulation/
13 (ovar$ adj3 stimulat$).tw.
14 (ovar$ adj3 hyperstimulat$).tw.
15 (ovar$ adj3 induc$).tw.
16 (ovulat$ adj3 induc$).tw.
17 (ovul$ adj3 stimulat$).tw.
18 (oocyte$ adj2 matur$).tw.
19 folliculogenesis.tw.
20 (ovar$ adj2 steroidogenesis).tw.
21 ((poor adj2 respon$) or poor prognos$).tw.
22 (low adj2 respon$).tw.
23 (recurrent adj2 failure$).tw
24 (poor adj2 reserve$).tw.
25 (infertil$ or subfe il$).tw.
26 assisted reprod cti$ techn$.tw.
27 (implant$ adj2 ail$).tw.
28 Bologna criteria.tw
29 or/1-28
30 exp Menotropins/
31 human menopausal gonadotrop?in$.tw.
32 pergonal.tw.
33 Menotrop?in$.tw.
34 (hMG or hphMG).tw.
35 (menopur$ or humegon).tw.
36 Merional-HG.tw.
37 or/30-36

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38 exp Follicle Stimulating Hormone/ and (recombinant or purified or urinary).tw.
39 recombinant follicle stimulating hormone$.tw.
40 recombinant FSH.tw.
41 (rec FSH or rFSH or rhFSH or hFSH or HPuFSH).tw.
42 (recFSH or Gonal F).tw.
43 (Human FSH or Fostimon).tw.
44 (purified adj2 FSH).tw.
45 (pFSH or p-FSH or hpFSH or hp-FSH).tw.
46 (Bemfola or follistim or Luveris).tw.
47 r-hFSH.tw.
48 FSH HP.tw.
49 purified Follicle Stimulating Hormone$.tw.
50 (urinary adj2 follicle stimulating hormone$).tw.
51 (uFSH or urinary FSH or u-FSH).tw.
52 (long acting adj3 FSH).tw.
53 (long acting adj2 follicle stimulating hormone$).tw.
54 daily FSH.tw.
55 (corifollitropin alpha or corifollitropin alfa).tw.
56 Elonva$.tw.
57 (follitropin beta or follitropin alpha or follitropin alfa).tw.
58 Ovaleap.tw.
59 (recombinant adj2 gonadotrop?in$).tw.
60 (urinary adj2 gonadotrop?in$).tw.
61 (purified adj2 gonadotrop?in$).tw.
62 rFSH LH.tw.
63 (recombinant LH or recombinant luteinizing hormone$).tw.
64 (rec LH or recLH).tw.
65 exogenous gonadotrop?in$.tw.
66 (gonadotrop?in$ adj1 urinary).tw.
67 (gonadotrop?in$ adj1 recombinant).tw.
68 (gonadotrop?in$ adj1 purified).tw.
69 growth hormone.tw.
70 or/38-69
71 (mild adj2 stimulation).tw.
72 (mild adj2 ivf).tw.
73 (microflare or flare).tw.
74 (ultrashort or ultra short).tw.
75 (agonist adj2 stop).tw.
76 stop lupron.tw.
77 (GNRHa or GNRH a or GNRH agonist$) t
78 (gonadotrop?in$ adj3 agonist$).tw.
79 (gonadotrop?in adj3 antagonist$) w.
80 (gonadotrop?in adj3 analog$).tw.
81 GNRH antagonist$.tw.
82 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin pamoate/
83 (buserelin or goserelin or leuprolide or nafarelin or triptorelin or zoladex).tw.
84 (deslorelin or histrelin).tw.
85 (suprefact or suprecor or supp lin or ovuplant or suprelorin).tw.
86 (abarelix or ganirelix or c trorelix) tw.
87 (degarelix or elag lix).tw.
88 (factrel or down egula ion).tw.
89 (cetrotide or lupron o synarel).tw.
90 GNRH analog$.tw.
91 (modified adj3 cycle$). w
92 (natural adj3 cycle$).tw.
93 MNC IVF.tw.
94 NCIVF.tw.
95 NC-IVF.tw.
96 minimal stimulat$.tw.
97 (stimulated adj2 cycle$).tw.
98 (unstimulated adj2 cycle$).tw.
99 (stimulat$ adj2 ivf).tw.

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100 unstimulated ivf.tw.
101 (unstimulated adj2 in vitro fertili?ation).tw.
102 (artificial adj3 cycle$).tw.
103 mini ivf.tw.
104 (mini adj2 in vitro fertili?ation).tw.
105 (minimal adj2 ivf).tw.
106 or/71-105
107 (protocol$ adj2 (mild or minimal or short or long or flare or stop or microflare)).tw.
108 (protocol$ adj2 (ultrashort or ultra short)).tw.
109 (protocol$ adj2 (ivf or rescue or multidose or modified or flexible)).tw.
110 (protocol$ adj2 (stimulat$ or unstimulat$)).tw.
111 (protocol$ adj2 (agonist$ or antagonist$)).tw.
112 (protocol$ adj2 (hyperstimulation or suppress$)).tw.
113 (protocol$ adj2 (standard or gonadotrop?in$)).tw.
114 (protocol$ adj2 (conventional or combined)).tw.
115 (protocol$ adj2 assisted reproduct$ techn$).tw.
116 or/107-115
117 37 or 70 or 106 or 116
118 29 and 117
119 randomized controlled trial.pt.
120 controlled clinical trial.pt.
121 randomized.ab.
122 randomised.ab
123 placebo.tw.
124 clinical trials as topic.sh.
125 randomly.ab.
126 trial.ti.
127 (crossover or cross-over or cross over).tw.
128 or/119-127
129 exp animals/ not humans.sh.
130 128 not 129
131 118 and 130

Appendix 4. Embase search strategy

From 1974 to present

Ovid platform

1 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/
2 embryo$ transfer$.tw.
3 in vitro fertili?ation.tw.
4 icsi.tw.
5 intracytoplasmic sperm injection$.tw.
6 (blastocyst adj2 transfer$).tw.
7 ivf.tw.
8 assisted reproduct$.tw.
9 exp infertility therapy/
10 superovulat$.tw.
11 COH.tw.
12 exp ovulation ind ction/
13 exp superovulat on/
14 (ovar$ adj3 stimulat$ .tw.
15 (ovar$ adj3 hypers mulat$).tw.
16 (ovar$ adj3 induc$).tw.
17 (ovulat$ adj3 induc$).tw.
18 (ovul$ adj3 stimulat$).tw.
19 (oocyte$ adj2 matur$).tw.
20 folliculogenesis.tw.
21 (ovar$ adj2 steroidogenesis).tw.
22 ((poor adj2 respon$) or poor prognos$).tw.
23 (low adj2 respon$).tw.
24 (recurrent adj2 failure$).tw.

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25 (poor adj2 reserve$).tw.
26 (infertil$ or subfertil$).tw.
27 or/1-26
28 exp human menopausal gonadotropin/
29 human menopausal gonadotrop?in$.tw.
30 pergonal.tw.
31 Menotrop?in$.tw.
32 (hMG or hphMG).tw.
33 menopur$.tw.
34 Merional-HG.tw.
35 hume?gon.tw.
36 or/28-35
37 exp follitropin/ and (recombinant or purified or urinary).tw.
38 recombinant follicle stimulating hormone$.tw.
39 recombinant FSH.tw.
40 (rec FSH or rFSH or rhFSH or hFSH or hpufsh).tw.
41 (recFSH or Gonal F).tw.
42 (Human FSH or Fostimon).tw.
43 (purified adj2 FSH).tw.
44 (pFSH or p-FSH or hpFSH or hp-FSH).tw.
45 Bemfola.tw.
46 r-hFSH.tw.
47 FSH HP.tw.
48 purified Follicle Stimulating Hormone$.tw.
49 (urinary adj2 follicle stimulating hormone$).tw.
50 (uFSH or urinary FSH or u-FSH).tw.
51 (long acting adj3 FSH).tw.
52 (long acting adj2 follicle stimulating hormone$).tw.
53 daily FSH.tw.
54 (corifollitropin alpha or corifollitropin alfa).tw.
55 Elonva$.tw.
56 (follitropin beta or follitropin alpha or follitropin alfa).tw.
57 follitropin beta.tw.
58 Ovaleap.tw.
59 (recombinant adj2 gonadotrop?in$).tw.
60 (urinary adj2 gonadotrop?in$).tw.
61 (purified adj2 gonadotrop?in$).tw.
62 rFSH LH.tw.
63 (recombinant LH or recombinant luteinizing hormone$).tw.
64 (rec LH or recLH).tw.
65 or/37-64
66 (modified adj3 cycle$).tw.
67 (natural adj2 cycle$).tw.
68 (MNC IVF or micro ivf or mini ivf).tw.
69 NCIVF.tw.
70 NC-IVF.tw.
71 ((unstimulated or stimulat$) adj2 cycle$).tw.
72 (stimulat$ adj2 ivf).tw.
73 (unstimulat$ adj2 ivf).tw
74 (artificial adj3 cyc e$).tw.
75 (unstimulated adj2 in vitro fertili?ation).tw.
76 MNC-FET.tw.
77 AC-FET.tw.
78 or/66-77
79 growth hormone.tw.
80 (mild adj2 stimulation).tw.
81 (microflare or flare).tw.
82 exogenous gonadotrop?in$.tw.
83 (gonadotrop?in$ adj1 urinary).tw.
84 (gonadotrop?in$ adj1 recombinant).tw.
85 (gonadotrop?in$ adj1 purified).tw.
86 (agonist adj2 stop).tw.

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87 (GNRHa or GNRH a or GNRH agonist$).tw.
88 (gonadotrop?in$ adj3 agonist$).tw.
89 GNRH antagonist$.tw.
90 (gonadotrop?in adj3 antagonist$).tw.
91 (gonadotrop?in adj3 analog$).tw.
92 exp gonadorelin/
93 exp buserelin/ or exp buserelin acetate/
94 exp goserelin/
95 exp leuprorelin/
96 exp nafarelin acetate/ or exp nafarelin/
97 exp triptorelin/
98 (buserelin or goserelin or leuprolide or nafarelin or triptorelin).tw.
99 (Zoladex or ganirelix or cetrorelix).tw.
100 (degarelix or elagolix).tw.
101 factrel.tw.
102 (cetrotide or lupron or synarel).tw.
103 GNRH analog$.tw.
104 or/79-103
105 (protocol$ adj2 (mild or minimal or short or long or flare or stop or microflare)) t .
106 (protocol$ adj2 (ultrashort or ultra short)).tw.
107 (protocol$ adj2 (ivf or rescue or multidose or modified or flexible)).tw.
108 (protocol$ adj2 (stimulat$ or unstimulat$)).tw.
109 (protocol$ adj2 (agonist$ or antagonist$)).tw.
110 (protocol$ adj2 (hyperstimulation or suppress$)).tw.
111 (protocol$ adj2 (standard or gonadotrop?in$)).tw.
112 (protocol$ adj2 (conventional or combined)).tw.
113 (protocol$ adj2 assisted reproduct$ techn$).tw.
114 or/105-113
115 36 or 65 or 78 or 104 or 114
116 27 and 115
117 Clinical Trial/
118 Randomized Controlled Trial/
119 exp randomization/
120 Single Blind Procedure/
121 Double Blind Procedure/
122 Crossover Procedure/
123 Placebo/
124 Randomi?ed controlled trial$.tw.
125 Rct.tw.
126 random allocation.tw.
127 randomly.tw.
128 randomly allocated.tw.
129 allocated randomly.tw.
130 (allocated adj2 random).tw.
131 Single blind$.tw.
132 Double blind$.tw.
133 ((treble or triple) adj blind$).tw.
134 placebo$.tw.
135 prospective study/
136 or/117-135
137 case study/
138 case report.tw
139 abstract report/ o etter/
140 or/137-139
141 136 not 140
142 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
143 141 not 142
144 116 and 143

Appendix 5. CINAHL search strategy

From 1982 to present

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Ebsco platform

#	Query
S49	S36 AND S48
S48	S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47
S47	TX allocat* random*
S46	(MH "Quantitative Studies")
S45	(MH "Placebos")
S44	TX placebo*
S43	TX random* allocat*
S42	(MH "Random Assignment")
S41	TX randomi* control* trial*
S40	TX ((singl* n1 blind*) or (singl* n1 mask*)) r X ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S39	TX clinic* n1 trial*
S38	PT Clinical trial
S37	(MH "Clinical Trials+")
S36	S17 AND S35
S35	S18 OR S19 OR S2 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34
S34	TX HMG o TX human menopausal
S33	TX uFS or TX urinary FSH or TX U FSH or TX urinary follicle stimulating
S32	TX pFSH or TX purified FSH or TX purified follicle stimulating
S31	TX R FSH or TX rfsh or TX rec fsh or TX recombinant FSH
S30	X gonadotrop?in N5 protocol*
S29	TX GNRH* N5 protocol*
S28	TX multidose N3 protocol*
S27	TX flexible N3 protocol*
S26	TX agonist N2 stop
S25	TX agonist* N3 protocol*

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(Continued)

S24	TX antagonist N3 protocol*
S23	TX microflare or TX flare
S22	TX modified cycle*
S21	TX natural cycle*
S20	TX mild N5 protocol*
S19	TX short N5 protocol*
S18	TX long N5 protocol*
S17	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
S16	TX natural cycle*
S15	TX (ovari* N2 induction)
S14	TX COH or TX poor respon*
S13	TX ovarian hyperstimulation
S12	TX superovulat*
S11	TX ovulation induc*
S10	TX assisted reproduct*
S9	(MM "Reproduction Techniques+")
S8	TX intracytoplasmic spe m injection*
S7	TX embryo* N3 transfer*
S6	T ovar* 3 hyperstimulat*
S5	TX ovari N3 stimulat*
S4	TX IVF or TX ICSI
S3	(MM "Fertilization in Vitro")
S2	TX vitro fertilization
S1	TX vitro fertilisation

HISTORY

Protocol first published: Issue 3, 2017

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CONTRIBUTIONS OF AUTHORS

Ioannis D Gallos (IDG) and Arri Coomarasamy (AC) conceived the idea for this study. Pedro Melo (PM), Abey Eapen (AE) and Mohammed Khairy (MK) performed abstract screening and full-text selection for inclusion. PM and AE extracted all study data and performed assessments of risk of bias and evidence certainty independently, with arbitration by AC where required. Aurelio Tobias (AT), Malcolm J Price (MJP) and PM designed and performed the pairwise and network meta-analyses. IDG drafted the protocol, and PM drafted the final review manuscript. MJP provided statistical advice and input. AE, Yealin Chung (YC), Yadava Jeve (YJ), Sesh Kamal Sunkara (SKS), Nick Macklon (NSM), Siladitya Bhattacharya (SB), Yacoub Khalaf (YK), Frank Broekmans (FJB), MK, IDG and AC provided important intellectual input and critically revised the final review manuscript.

DECLARATIONS OF INTEREST

Pedro Melo: supported by a grant awarded by the Tommy's Charity, who funds the Tommy's National Centre for Miscarriage Research.

AE: none declared.

YC: supported by a grant awarded by the Tommy's Charity, who funds the Tommy's National C tre for Miscarriage Research.

YJ: none declared.

MJP: none declared.

SKS: co-investigator for Sunkara 2014. SKS did not participate in any decisions regarding t is trial. She has received fees for lectures/ symposia organised by Merck and Ferring.

NSM: co-investigator for Hohmann 2003. NSM did not participate in any decisions regarding this trial. He has advised a number of pharmaceutical companies on product development and has lectured at symposia sponsored by a number of pharmaceutical companies that produce gonadotrophins, for which he has received honoraria. He has r ceiv d consultancy fees from Ferring.

SB: none declared.

YK: co-investigator for Sunkara 2014. YK did not participate in any ecis on regarding this trial. No other conflicts of interest declared.

AT: none declared.

FJB: co-investigator for Hompes 2008. FJB did not participate i any decisions regarding this trial. No other conflicts of interest declared.

MK: none declared.

IDG: none declared.

AC: co-investigator for Sunkara 2014. AC did not particip e in any decisions regarding this trial. No other conflicts of interest declared.

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- Tommy's National Centre for Miscarriage R search, UK

External sources

- National Institute for Health Resear h (NIHR), UK

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CHAPTER 3: SERUM LUTEAL PHASE PROGESTERONE IN WOMEN UNDERGOING FROZEN EMBRYO TRANSFER IN ASSISTED CONCEPTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Preamble

Chapter 2 identified a substantial reduction in OHSS rates when women with predicted normal or high response to COS receive short GnRH antagonist protocols versus long GnRH agonist protocols. In recent years, the rise in FET cycle numbers has further contributed to a reduction in OHSS, as discussed in the introduction. Chapter 3 focuses specifically on the association between serum luteal phase progesterone and treatment outcomes in FET.

This chapter was published in *Fertility and Sterility* in 2021. Appendix 2 of this thesis contains the supplemental files for this publication.

Authors' contributions

Dr Pedro Melo led all stages of the review process. Dr Melo and Professor Coomarasamy designed the study and wrote the protocol. Dr Melo, Dr Chung and Mrs Pickering performed the searches, abstract screening and full-text selection. Dr Melo and Dr Chung undertook the data extraction, synthesis and quality assessment. Dr Melo and Professor Price carried out the data analyses. Dr Melo, Professor Coomarasamy, Professor Gallos and Professor Price wrote the final draft of the manuscript. Dr Chung, Mrs Pickering, Professor Fishel, Dr Khairy, Professor Kingsland, Dr Lowe, Dr Petsas, Dr Rajkhowa, Dr Sephton, Dr Tozer, Dr Labarta, Dr Wilcox and Professor Devall provided critical input into the final manuscript. All authors approved the final version and accept responsibility for the paper as published.

Page 39. Serum luteal phase progesterone in women undergoing frozen embryo transfer in assisted conception: a systematic review and meta-analysis

ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Serum luteal phase progesterone in women undergoing frozen embryo transfer in assisted conception: a systematic review and meta-analysis

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Objective: To investigate the association between luteal serum progesterone levels and frozen embryo transfer (FET) outcomes.
Design: Systematic review and meta analysis.
Setting: Not applicable.
Patient(s): Women undergoing FET.
Intervention(s): We conducted electronic searches of MEDLINE, PubMed, CINAHL, EMBASE, the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and grey literature (not widely available) from inception to March 2021 to identify cohort studies in which the serum luteal progesterone level was measured around the time of FET.
Main Outcome Measure(s): Ongoing pregnancy or live birth rate, clinical pregnancy rate, and miscarriage rate.
Result(s): Among the studies analyzing serum progesterone level thresholds <10 ng/mL, a higher serum progesterone level was associated with increased rates of ongoing pregnancy or live birth (relative risk [RR] 1.47, 95% confidence interval [CI] 1.28 to 1.70), higher chance of clinical pregnancy (RR 1.31, 95% CI 1.16 to 1.49), and lower risk of miscarriage (RR 0.62, 95% CI 0.50 to 0.77) in cycles using exclusively vaginal progesterone and blastocyst embryos. There was uncertainty about whether progesterone thresholds ≥ 10 ng/mL were associated with FET outcomes in sensitivity analyses including all studies, owing to high interstudy heterogeneity and wide CIs.
Conclusion(s): Our findings indicate that there may be a minimum clinically important luteal serum concentration of progesterone required to ensure an optimal endocrine milieu during embryo implantation and early pregnancy after FET treatment. Future clinical

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P.M. has nothing to disclose. Y.C. has nothing to disclose. O.P. has nothing to disclose. M.J.P. has nothing to disclose. S.F. is a minor shareholder of CARE Fertility, but has no financial or other interest with progesterone testing or manufacturing companies. M.K. has nothing to disclose. C.K. has nothing to disclose. P.L. reports personal fees from Pharmasure, outside the submitted work. G.P. reports personal fees from Besins Healthcare, outside the submitted work. M.R. has nothing to disclose. V.S. has nothing to disclose. A.T. has nothing to disclose. S.W. has nothing to disclose. E.L. was the lead author in two of the manuscripts in this review (Labarta et al.[26]; and Labarta et al.[28]). She has additionally received a grant from Ferring in 2020, has provided consultancy services for MSD and Ferring Pharmaceuticals, and is part of the Ferring Pharmaceuticals LIFE program and Merck Global program for Fertility Innovation Leaders. During the past 12 months, E.L. has received honoraria from Angelini/IBSA, Gedeon Richter, and Ferring Pharmaceuticals for lecturing. M.W. reports personal fees from Ferring Pharmaceuticals, outside the submitted work. A.D. has nothing to disclose. I.G. has nothing to disclose. A.C. has conducted two trials evaluating the role of progesterone in miscarriage prevention (the PROMISE trial, published in 2015 [85]; and the PRISM trial, published in 2019 [75]). However, he has no financial or other interest with progesterone testing or manufacturing companies.
Supported by a doctoral research fellowship awarded by the Tommy's Charity and the University of Birmingham (to P.M.). M.J.P. is supported by the National Institute for Health Research Birmingham Biomedical Research Centre.
The views expressed are those of the investigators and not necessarily those of the NHS, NIHR or the Department of Health and Social Care.
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trials are required to assess whether administering higher dose luteal phase support improves outcomes in women with a low serum progesterone level at the time of FET.
PROSPERO Number: CRD42019157071 (Fertil Steril® 2021;■:■ ■. ©2021 by American Society for Reproductive Medicine.)
Key Words: Endometrial receptivity, frozen embryo transfer, luteal phase support, live birth, miscarriage, progesterone

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/32820

The use of freeze-thaw embryo transfer (FET) treatment is an important option in assisted conception practice. Freeze-thaw embryo transfer allows clinicians to comply with single-embryo transfer policies while significantly reducing the chance of ovarian hyperstimulation syndrome associated with controlled ovarian stimulation (1). Furthermore, it is thought that FET mitigates the risk of endometrial asynchrony by avoiding the need for treatment with gonadotropins and by allowing greater flexibility on the timing of embryo transfer (2). For these reasons, some clinics have started to offer a universal freeze-all policy (3). According to the Human Fertilisation and Embryology Authority, the number of FETs undertaken in the United Kingdom nearly doubled between 2013 and 2018, now accounting for 38% of all in vitro fertilization (IVF) cycles. Conversely, the number of fresh embryo transfers decreased by 11% in the same time period (4). This mirrors similar trends in continental Europe (5), the United States (6), and across the world (7). The success rate of FET cycles remains relatively low nonetheless, with fewer than one in three women achieving a live birth after FET treatment worldwide (7).

There has been a growing body of research aimed at identifying ways to predict and improve FET outcomes in the past decade. It is widely accepted that treatment success depends on a plethora of factors including the embryo ploidy status and endometrial receptivity (8). Endometrial thickness as measured by ultrasound has been used historically as a marker of receptivity, whereas recent studies have focused on identifying receptive molecular patterns through histologic and transcriptomic analyses of the endometrial tissue (9, 10). Despite these advances, there remains a significant level of uncertainty about strategies to optimize day-to-day clinical practice and increase the success rates in FET. For example, there is no consensus on how to best prepare the endometrium for embryo implantation in freeze-thaw treatment (2). Some investigators advocate that in ovulatory women it is optimal to transfer the embryo in the midluteal phase of a natural cycle without administering exogenous hormones (NC-FET), whereas others support the artificial preparation of the endometrium with hormone replacement therapy (HRT-FET). To date, however, both approaches have been shown to be largely equivalent in effectiveness and safety (11–14).

There is some evidence that the circulating progesterone level may be associated with treatment success in FET (15–17). Progesterone is a steroid hormone produced by the corpus luteum shortly after ovulation in a natural menstrual cycle. It is through the regulatory effect of progesterone that the endometrium becomes secretory and receptive to the implanting embryo during a four-day interval in the luteal phase of the menstrual cycle termed the "window of implantation" (18). Before or after this strictly timed interval, implanting embryos face an asynchronous endometrium where the immune-endocrine milieu may impede rather than facilitate implantation (19). Serum progesterone levels peak during the window of implantation and have been used as a marker of endometrial receptivity in natural conception and assisted reproductive technology (ART) treatment (20). During the follicular phase, a high circulating progesterone level identifies premature luteinization and endometrial asynchrony (21–23). By contrast, in the luteal phase, it has been suggested that single progesterone level measurements <10 ng/mL indicate luteal phase deficiency, which in turn has been associated with infertility and recurrent pregnancy loss (24). Further, fresh IVF cycles have long been known to lack endogenous progesterone support in the luteal phase mainly because of the inhibition of luteinizing hormone secretion. The administration of exogenous hormones such as progesterone remains therefore critical to achieve treatment success in IVF (25).

The hypothesis that serum progesterone levels may be associated with FET success stems from data linking a higher circulating progesterone level with increased live birth rates and reduced risk of miscarriage in freeze-thaw cycles (26–28). In addition, some researchers postulate that women with a low serum progesterone level may benefit from additional progesterone supplementation to achieve optimal luteal phase support (LPS), although good-quality interventional evidence remains scarce (29, 30). Existing data are conflicting, however, with other studies suggesting that excessive progesterone may be equally as detrimental to treatment outcomes as low progesterone (15, 31, 32). It remains therefore unclear whether serum progesterone levels may constitute a reliable predictor of FET outcomes, and whether additional progesterone supplementation in women with low circulating levels may lead to luteal rescue and improved treatment success. The aim of this systematic review and meta-analysis was to summarize and appraise published data on the association between circulating progesterone levels in the luteal phase and treatment outcomes in FET cycles.

MATERIALS AND METHODS

Registration

This review was registered with PROSPERO (CRD42019157071) before commencement.

Search Strategy

We performed extensive bibliographic searches according to the Preferred Reporting Items for Systematic Reviews and

Meta-Analysis guidelines (33). The following computerized databases were searched from their inception until March 15, 2021: MEDLINE, PubMed, CINAHL, EMBASE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and grey literature (not widely available). The key MeSH/Emtree expressions and search terms (and respective word variants) used to identify studies investigating serum progesterone levels inFET cycles were the following: progesterone AND (in vitro fertilization OR intracytoplasmic sperm injection, frozen embryo, embryo transfer, assisted reproduction techniques). The search strategy was reviewed by two medical sciences librarians. Additional studies were identified from the reference lists of selected abstracts and articles to avoid missing relevant data. We applied no language restrictions to any of our searches.

Study Selection and Quality Assessment

We selected studies in a two-step process using Covidence (34). Two independent reviewers (P.M. and Y.C., or P.M. and O.P.) performed the study selection, first by assessing the titles and then by screening the abstracts of selected citations. The full articles of studies that were deemed likely to meet our eligibility criteria were obtained. Any disagreements about inclusion were resolved by consensus or arbitration by a third investigator (A.C.).

We included observational studies investigating the relationship between serum progesterone levels around the time of FET and treatment outcomes. In natural FET cycles, we included publications in which the serum progesterone level was measured at any time in the luteal phase of the participants' menstrual cycles. In HRT-FET cycles, because of variation in existing HRT regimens for endometrial preparation and differences in study protocols, we included articles in which the serum progesterone levels were measured at any time from the onset of exogenous progesterone supplementation (by any route available) to at least the first pregnancy test after embryo transfer.

We excluded studies performed solely in fresh cycles or in which serum progesterone level measurement was undertaken as part of a trial (for example, comparing different routes of progesterone administration) but not directly correlated with treatment outcomes. In addition, we excluded interventional studies in which women with a low serum progesterone level around the time of FET received additional LPS, either by increasing the progesterone dosage or by adding a progestogen with a different route of administration. All articles meeting the selection criteria underwent quality assessment using the Newcastle-Ottawa scale for quality assessment of observational studies by two independent reviewers (P.M. and Y.C.), as recommended by the Cochrane Collaboration (35, 36).

Study Outcomes

The primary outcome of interest was the composite rate of ongoing pregnancy or live birth (OPR or LBR) per cycle. Ongoing pregnancy was defined as a viable intrauterine pregnancy of at least 12 weeks' gestation confirmed on ultrasound, whereas live birth was defined as the delivery of a live fetus after 22 completed weeks of gestational age (37). Secondary outcomes included the clinical pregnancy rate (CPR) per cycle, defined as the presence of one or more gestational sacs on ultrasound; the miscarriage rate (MR) per pregnancy, defined as the spontaneous loss of an intrauterine pregnancy before 22 completed weeks of gestation (37); and the rate of adverse events attributable to exogenous progesterone supplementation (e.g., abdominal pain, bloating, nausea, depression, and headache).

Data Extraction Process

Two investigators (P.M. and Y.C.) independently extracted data from the eligible studies, including publication date, country of origin, study objective, participants (number and demographic characteristics), methods and statistical analysis, study findings, and study conclusions. Disagreements were resolved by consensus or arbitration by a third reviewer (A.C.).

Data Synthesis and Analysis

All data analyses were performed using Stata Statistical Software (Release 16, TX, USA). We described effect sizes using relative risk (RR) and 95% confidence intervals (CI). We assessed statistical heterogeneity by measure of the I^2 statistic and set the acceptability of heterogeneity at $I^2<50\%$, in line with the recommendations from the Cochrane handbook (36). We performed meta-analyses of dichotomous outcomes using a random effects model.

Where studies reported progesterone concentrations in nanomoles per liter, we converted them to nanograms per milliliter (conversion factor 3.18), because this is how the serum progesterone level was expressed in most of the included papers. For the purposes of the meta-analysis, we grouped studies according to the serum progesterone thresholds they reported (<10, 10–20, >20–30, and >30 ng/mL). We dichotomized the outcome data according to whether they pertained to "high" or "low" serum progesterone level as defined by each study (i.e., respectively above or below the threshold specified for the serum progesterone level in each individual study). Where investigators reported adjusted effect estimates to evaluate the impact of confounders on their crude analyses (e.g., adjusted odds ratios [aOR]), we conducted meta-analyses to investigate the pooled adjusted effect size of "low" serum progesterone level vs. "high" serum progesterone level according to the specified cutoff.

Subgroup Analyses and Sensitivity Analyses

The primary analysis included studies in which only blastocysts were used in FET treatment. In addition, we planned to analyze the data according to the route of progesterone administration if a sufficient number of studies were available (intramuscular [IM], oral [PO], rectal [PR], subcutaneous [SC], or vaginal [PV]). We performed sensitivity analyses for all outcomes of interest (OPR or LBR, CPR, and MR) to determine whether our conclusions were robust to arbitrary decisions regarding eligibility and analysis. The sensitivity analyses

aimed to assess whether our conclusions would have differed if eligibility for the meta-analyses had been restricted to studies at low risk of bias; and if all studies had been included in the meta-analysis, regardless of cycle type (NC-FET and HRT-FET), progesterone route (IM, PO, PV, PR, and SC), stage of embryo development (cleavage and blastocyst), or risk of bias.

RESULTS

Search Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Flow Diagram (Supplemental Fig. 1, available online) shows the details of the study selection process. The systematic search on March 15, 2021, identified 4,974 articles, which were imported into Covidence. After the removal of duplicates, 3,639 titles and abstracts were screened, of which 3,586 were excluded as they were clearly not relevant. One study was ongoing (38). The remaining 52 articles underwent full-text screening, and 31 were excluded for the following reasons: 7 studies were interventional; 7 did not correlate progesterone levels with treatment outcomes; 4 were review or commentary papers; 2 measured the serum progesterone level before the luteal phase (Supplemental Table 1, available online); and 11 studies are awaiting classification because of unanswered or unsuccessful correspondence with the investigators (Supplemental Table 2). We included 21 studies in the narrative synthesis, 16 of which were suitable for meta-analysis. We contacted the investigators of 32 articles to obtain additional study details and data (Supplemental Table 2). To date, we have received responses for 10 publications (15, 26–28, 39–44).

Included Studies

Study characteristics. Table 1 contains a detailed description of the 21 included studies. All included manuscripts were cohort studies, of which 8 were prospective (26, 28, 43, 45–49) and 13 were retrospective (15, 17, 27, 31, 32, 40–42, 44, 50–53). Twenty studies were published as full articles (15, 17, 26–28, 31, 32, 40–45, 47–53) and one as a conference abstract (46). Five of the included studies were conducted in Spain (26–28, 50, 52); three in Japan (32, 44, 47); two each in Australia (15, 51), Denmark (17, 45), France (40, 41), and Turkey (42, 43); and one each in China (53), India (46), Iran (49), Iraq (48), and the United States (31). Eighteen studies focused solely on HRT-FET cycles; two included HRT-FET and fresh donor recipient cycles (26, 28); and one study included only NC-FET cycles (52). Finally, although the largest publication featured results from both HRT-FET and NC-FET cycles, only the HRT-FET data were suitable for meta-analysis (51).

In aggregate, the quantitative synthesis included 6,175 FET cycles, of which 5,881 were HRT-FET and 294 were NC-FET. The participants were aged between 18 and 50 years, and the body mass index (BMI) of included women ranged from 18 to 37 kg/m^2. Furthermore, 11 studies analyzed autologous cycles only (15, 17, 27, 31, 41, 42, 45, 49, 50, 52, 53), whereas 1 publication focused exclusively on donor cycles (26) and 2 included both autologous and donor cycles (28, 51). The oocyte source was not specified in the remainder of the included articles.

Most of the included studies (n = 15) analyzed cycles including only day 5/6 blastocysts; four studies included both cleavage-stage and blastocyst embryos (32, 40, 47, 51); and two publications analyzed exclusively cleavage-stage embryos (48, 53). Three of the included studies analyzed FET cycles using euploid embryos only (31, 43, 50), whereas in the remaining studies the ploidy status of the embryos was not specified.

Serum progesterone level measurement. The timing of serum progesterone level measurement varied across all the included studies. Ten studies measured the progesterone level on the day of FET (26, 28, 31, 32, 42, 43, 46–49), 3 measured the serum progesterone level on the day before FET (27, 50, 52), and 1 study one or two days before transfer (41). The remaining studies tested the progesterone levels later on in the luteal phase: one study two to three days after FET (15); one 16 days after the onset of progesterone supplementation (51); three studies measured the progesterone level on the day of the pregnancy test (17, 45, 53); and in one study, the progesterone level was tested on the day of the pregnancy test and then again 46 hours and 96 hours later (40). Finally, one study measured the serum progesterone level every five days from the day after FET until 9 weeks 1 day gestation (44).

Twelve studies reported on the time interval between the last dose of progesterone and venepuncture in HRT-FET cycles (15, 17, 26, 27, 28, 31, 42, 45, 47–50). Of these, 10 studies were included in the quantitative synthesis, with dose-to-measurement intervals ranging between 1 and 12 hours (15, 17, 26, 28, 31, 42, 45, 47, 49, 50).

In addition, there was variation in the progesterone cutoff levels reported, which ranged between 5 ng/mL (32) and 53.2 ng/mL (43). The most common threshold was 8.8 ng/mL, used in two studies (28, 45). Eight studies reported on treatment outcomes according to serum progesterone level percentile analyses (42, 43, 45, 47, 49–51, 53); three studies reported on progesterone thresholds using a "high" vs. "low" dichotomy (26, 28, 51); three publications reported thresholds according to previously published literature or what the investigatos perceived to be accepted standard practice (17, 31, 52); one study reported outcomes according to a receiver operating characteristic curve analysis of serum progesterone levels (46); and in two manuscripts, no rationale was given for the reported progesterone level thresholds (15, 32). Finally, two publications identified a linear positive correlation between serum progesterone level and live birth without a significant cutoff point associated with treatment success (27, 44).

Ten of the included studies reported on intraassay and interassay coefficients of variation associated with serum progesterone level measurements, ranging between 1.2% and 23.1% (15, 17, 26–28, 42, 43, 45, 49, 52). In the remaining studies, this was not stated.

Outcomes. Twelve publications reported on live birth (15, 27, 28, 31, 44, 46, 47, 49–53). However, the gestational age threshold to define this outcome varied between >20 weeks in two studies (15, 51), >22 weeks in another two

TABLE 1

Characteristics of the included studies.

Source	Study design and duration	Autologous/ donor cycles	Inclusion criteria	Exclusion criteria	HRT-FET/ NC-FET	Number of FET cycles analyzed	Progesterone route of administration and dose	Embryo stage at the time of transfer	Embryo ploidy status	Timing of progesterone measurement	Progesterone cutoff values (ng/mL)	Intra-/ inter-assay variability range	Outcomes	Main findings	Included in meta-analysis
Yovich et al. (15)	Retrospective cohort (Jan 2008 to Dec 2013)	Autologous	Age 22–49 years; HRT-FET; SET	BMI >37 kg/m^2; pelvic pathology	HRT-FET	529	PV micronized capsules 400 mg TDS; continued until 10 weeks of gestation	Day 5/6 blastocysts	Unstated	2–3 days after FET (Day 8–9 of progesterone administration) 2–4 h after progesterone administration	<9.43 (n 30); 9.43–15.41 (n 147); 15.72–21.70 (n 169); 22.01–31.13 (n 111); ≥31.45 (n 72)	<5%	Clinical pregnancy Live birth	Progesterone levels ranging between 22.01 and 31.13 ng/mL were associated with higher CPR (64%, *P* .005) and LBR (50%, *P* .031) compared with values <22.01 ng/mL (CPR 48.8% and LBR 37.3%) For progesterone >31.45 ng/mL, the CPR dropped to 44% (*P* .047) and there was a nonsignificant reduction in LBR to 36% (*P*>.05) There were no differences in the MR between the different strata of serum progesterone levels	Yes
Kofinas et al. (31)	Retrospective cohort (2010 to 2013)	Autologous	Euploid embryos; SET	Donor cycles; frozen oocyte cycles; progesterone supplementation other than IM	HRT-FET	213	IM 50 or 75 mg OD; continued until 9 weeks of gestation	Day 5/6 expanded blastocysts	Euploid	Day of FET (Day 6 of progesterone administration) Approximately 12 h after IM injection	<20; ≥20	Unstated	Pregnancy Clinical pregnancy Miscarriage Ongoing pregnancy Live birth	Women with progesterone ≥20 ng/mL had lower OPR/LBR (45% vs. 65%, *P* .02) and higher MR (27% vs. 12%, *P* .01) than women with progesterone <20 ng/mL	No—no absolute denominator values. Correspondence with the investigators remained unanswered
Akaeda et al. (32)	Retrospective cohort (Sep 2010 to Sep 2015)	Unspecified	First HRT-FET cycle	Repeat FET cycles	HRT-FET	123	PV tablets 100 mg BD or TDS; continued until 8 weeks of gestation	Day 2/3 (n 82); day 5 blastocysts (n 41)	Unstated	Day of FET (Day 2, 3 of progesterone for cleavage embryos; day 6 of progesterone for blastocysts) Time from progesterone administration not specified	<5.0 (n 13); 5.0–9.9 (n 55); 10.0–14.9 (n 40); ≥15.0 (n 15)	Unstated	Clinical pregnancy	Women whose progesterone level was 5.0 to 9.9 ng/mL had the highest CPR in comparison with the remainder of the cohort (32.7% vs. 20.6%, respectively), although there was statistical uncertainty in this finding (*P* .13)	Yes

Melo. Serum progesterone in FET cycles. Fertil Steril 2021.

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Source	Study design and duration	Autologous/ donor cycles	Inclusion criteria	Exclusion criteria	HRT-FET/ NC-FET	Number of FET cycles analyzed	Progesterone route of administration and dose	Embryo stage at the time of transfer	Embryo ploidy status	Timing of progesterone measurement	Progesterone cutoff values (ng/mL)	Intra-/ inter-assay variability range	Outcomes	Main findings	Included in meta-analysis
Labarta et al. (26)	Prospective cohort (Feb to Oct 2016)	Donor	Age <50 years; BMI <30 kg/m^2; first or second donor cycle; no systemic conditions; triple layer endometrium >6.5 mm after HRT; 1–2 good-quality blastocysts	RM/RIF; severe male factor; uterine pathology; hydrosalpinx	HRT-FET	125 (Total study sample included additional 86 fresh donor cycles, total n 211)	PV micronized capsules 400 mg BD; continued until 12 weeks of gestation	Day 5/6 blastocysts	Unstated	Day of FET (Day 6 of progesterone administration) 4–5 h after progesterone administration	<9.2 (n 33); ≥9.2 (n 92)	2.4%–5.5%	Implantation rate Clinical pregnancy Miscarriage Ongoing pregnancy	Analysis of the total cohort (HRT-FET and fresh donor oocyte cycles) identified higher OPR in women with progesterone ≥9.2 mg/mL ("high") vs. those with progesterone <9.2 ng/mL ("low") (OPR 52.8% vs. 32.7%, respectively, *P* .016) In the subgroup undergoing HRT-FET only (n 125), the difference in OPR between women with high and low progesterone did not reach statistical significance (48.9% vs. 33.3%, respectively, *P* .12) The investigators' findings were less certain about the difference in MR between those with high and low progesterone in the total cohort (20% vs. 34.6%, respectively, *P* .124) and in the HRT-FET subgroup (30% vs. 42%, respectively, *P* .31)	Yes
Basnayake et al. (51)	Retrospective cohort (Jan 2000 to Dec 2014)	Mixed	SET	Cases in which serum progesterone level was not recorded;	HRT-FET (n 1,580); NC-FET (n 3,002)	1,580 (HRT only)	PV micronized gel 8%, 90 mg OD or BD or PV compounded progesterone	Day 3–5	Unstated	Day 16 of progesterone supplementation Time from progesterone	≤15.72 (n 1,349); >15.72 (n 231)	Unstated	Clinical pregnancy Miscarriage Live birth	Women with higher serum progesterone level (>15.72 ng/mL) experienced	Yes

Melo. Serum progesterone in FET cycles. Fertil Steril 2021.

TABLE 1

Continued.

Source	Study design and duration	Autologous/ donor cycles	Inclusion criteria	Exclusion criteria	HRT-FET/ NC-FET	Number of FET cycles analyzed	Progesterone route of administration and dose	Embryo stage at the time of transfer	Embryo ploidy status	Timing of progesterone measurement	Progesterone cutoff values (ng/mL)	Intra-/ inter-assay variability range	Outcomes	Main findings	Included in meta-analysis
				ethinyl estradiol supplementation; IM or PR progesterone			capsules 200–400 mg BD or TDS or PV capsules 100 mg BD or TDS; continued until 12 weeks of gestation			administration not specified				increased CPR (30.3% vs. 16.8%, crude OR 2.15, 95% CI 1.55 to 2.98), higher LBR (26.4% vs. 11.3%, crude OR 2.80, 95% CI 1.97 to 3.98), and lower MR (14.3% vs. 32.6%, crude OR 0.34, 95% CI 0.16 to 0.74)	
Alsbjerg et al. (17)	Retrospective cohort (Jan 2016 to Dec 2017)	Autologous	Age <45 years; BMI <35 kg/m^2; autologous blastocysts	Oocyte donor cycles; IM progesterone; cleavage-stage embryo transfers	HRT-FET	244	PV micronized gel 8%, 90 mg TDS; duration of progesterone not stated	Day 5/6 blastocysts	Unstated	9–11 days after FET (day of pregnancy testing) (Day 15–17 of progesterone administration) 1–3 h after progesterone administration	<11.00 (n 125); ≥11.00 (n 119)	<5%	Clinical pregnancy Miscarriage Ongoing pregnancy	Reduction in OPR (crude OR 0.59, 95% CI 0.34 to 0.99, *P* .04) and CPR (crude OR 0.57, 95% CI 0.03 to 0.96, *P* .03) in women with lower progesterone (<11.00 ng/mL) compared with those with higher progesterone (≥11 ng/mL) No difference identified in MR between groups (crude OR 1.28, 95% CI 0.64 to 2.56, *P*>.05)	Yes
Kawachiya et al. (44)	Retrospective cohort (Jun 2009 to Apr 2017)	Unspecified	SET; women with clinical pregnancy (gestational sac visible on ultrasound at 4–5 weeks' gestation) after HRT-FET	Monozygotic twinning; voluntary termination of pregnancy	HRT-FET	120	PO dydrogesterone 30 mg/day; PO ethinyl estradiol and norgestrel 0.5 mg added in the luteal phase; continued until positive pregnancy test	Blastocysts	Unstated	From the day after FET until 9w1d gestation, every five days Time from progesterone administration not specified	None identified	Unstated	Miscarriage Live birth	Progesterone level rose exponentially in those who had a live birth, whereas it plateaued in women who sustained a miscarriage The investigators did not identify an optimal cutoff or range of serum progesterone levels associated with higher LBR	No
Gaggiotti-Marre et al. (50)	Retrospective cohort (Jan 2016 to Jun 2017)	Autologous	Euploid blastocysts	Uterine pathology; donor cycles; mosaic embryos	HRT-FET	244	PV micronized capsules 200 mg TDS; duration of	Blastocysts	Euploid	Day before FET (Day 4 of progesterone administration)	≤8.06 (n 61); 8.07–10.64 (n 61); 10.65–13.13	Unstated	Pregnancy Miscarriage Live birth	Women in the lowest progesterone level quartile	Yes

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TABLE 1

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Source	Study design and duration	Autologous/ donor cycles	Inclusion criteria	Exclusion criteria	HRT-FET/ NC-FET	Number of FET cycles analyzed	Progesterone route of administration and dose	Embryo stage at the time of transfer	Embryo ploidy status	Timing of progesterone measurement	Progesterone cutoff values (ng/mL)	Intra-/ inter-assay variability range	Outcomes	Main findings	Included in meta-analysis
							progesterone not stated			4–6 h after progesterone administration	(n 61); >13.13 (n 61)			(≤8.06 ng/mL) had higher MR than women in the upper three progesterone level quartiles (>8.06 ng/mL; 32.4% vs. 13.5%, respectively, *P* .021) and lower LBR (41.0% vs. 59.6%, respectively, *P* .046) MR was reduced in those with progesterone >10.64 ng/mL (9.5% vs. 26.6%, *P* .07); in addition, this group had higher LBR vs. women with progesterone ≤10.64 ng/mL (62.3% vs. 47.5%, *P* .029)	
Kakkad et al. (46)	Prospective cohort (interim analysis)	Unspecified	HRT-FET	Unspecified	HRT-FET	130	IM micronized 100 mg/day PV micronized progesterone and PO dydrogesterone after embryo transfer; duration of progesterone not stated	Blastocysts	Unstated	Day of FET (Day 6 of progesterone administration) Time from progesterone administration not specified	≤25.1 (n 54); >25.1 (n 76)	Unstated	Pregnancy Miscarriage Ongoing pregnancy Live birth	Women with progesterone level >25.1 ng/mL had higher OPR/LBR than those with progesterone ≤25.1 ng/mL (63.2% vs. 27.8%, respectively, *P*< .001) MR did not significantly differ between groups (5.9% vs. 11.1%, respectively, *P* .23)	Yes
Boynukalin et al. (43)	Prospective cohort (Mar to Aug 2018)	Unspecified	HRT-FET; euploid day 5 blastocysts; SET	Uterine pathology; hydrosalpinx; ET <7 mm after HRT; embryos biopsied on day 6	HRT-FET	168	IM 100 mg/day; duration of progesterone not stated	Day 5 blastocysts	Euploid	Day of FET (Day 4 or 5 of progesterone administration) Time from progesterone administration not specified	<13.6 (n 42); 13.6–24.3 (n 43); 24.4–53.2 (n 42); >53.2 (n 41)	2.4%–3.9%	Pregnancy Clinical pregnancy Miscarriage Ongoing pregnancy	CPR was lower in women with progesterone level in the first quartile (<13.6 ng/mL) when compared with that in participants with	Yes

Melo. Serum progesterone in FET cycles. Fertil Steril 2021.

TABLE 1

Continued.

Source	Study design and duration	Autologous/ donor cycles	Inclusion criteria	Exclusion criteria	HRT-FET/ NC-FET	Number of FET cycles analyzed	Progesterone route of administration and dose	Embryo stage at the time of transfer	Embryo ploidy status	Timing of progesterone measurement	Progesterone cutoff values (ng/mL)	Intra-/ inter-assay variability range	Outcomes	Main findings	Included in meta-analysis
														levels in the three upper quartiles (≥13.6 ng/mL, 35.7% vs. 73.8%, respectively, *P*< .001) Women with progesterone level ≥13.6 ng/mL additionally had higher OPR (69.8% vs. 26.2%, respectively, *P*< .001) and lower MR (5.4% vs. 26.7%, respectively, *P* .015) than those with progesterone level <13.6 ng/mL	
Polat et al. (42)	Retrospective cohort (Oct 2017 to Oct 2019)	Autologous	Age 20–44 years; BMI ≤35 kg/m^2; first FET cycle only	PGT-A/MD/SR	HRT-FET	475 (PV progesterone only, n 143; PV and IM progesterone, n 332)	Oct 2017 to Feb 2018 (n 143): PV gel 8% BD; Mar 2018 to Oct 2019 (n 332): IM 50 mg every three days; and PV gel 8% BD; continued until 10 weeks of gestation	Day 5/6 blastocysts	Unstated	Day of FET (Day 6 of progesterone administration) 4–5 h after progesterone administration	PV group: <8.75 (n 14); 8.76–12.94 (n 57); 12.95–20.42 (n 58); >20.42 (n 14). PV and IM group: <11.75 (n 33); 11.76–19.86 (n 133); 19.87–31.79 (n 133); >31.79 (n 33)	3.1%–24.3%	Pregnancy Implantation rate Clinical pregnancy Miscarriage Ongoing pregnancy	No correlation identified between serum progesterone level and CPR, OPR, or MR	Yes
Alsbjerg et al. (45)	Prospective cohort (Mar 2018 to Apr 2019)	Autologous	Age 18–46 years; BMI <34 kg/m^2; SET; autologous embryos	Oocyte donor cycles; IM progesterone; uterine pathology; severe comorbidities	HRT-FET	239	PV micronized gel 8%, 90 mg BD and PR micronized progesterone gel 8%, 90 mg/day; continued both until 7 weeks, then PV only until 10 weeks of gestation	Day 5/6 blastocysts	Unstated	9–11 days after FET (day of pregnancy testing) (Day 15–17 of progesterone administration) 1–8 h after progesterone administration	<8.8 (n 25); 8.8–14.2 (n 96); >14.2 (n 118)	<5%	Pregnancy Clinical pregnancy Miscarriage Ongoing pregnancy	Women whose progesterone levels were <8.8 ng/mL or >14.2 ng/mL had lower OPR (36% and 39%, respectively) than women with intermediate levels (8.8–14.2 ng/mL, OPR 53%), but this did not reach statistical significance (*P*	Yes

Melo. Serum progesterone in FET cycles. Fertil Steril 2021.

TABLE 1

Continued.

Source	Study design and duration	Autologous/ donor cycles	Inclusion criteria	Exclusion criteria	HRT-FET/ NC-FET	Number of FET cycles analyzed	Progesterone route of administration and dose	Embryo stage at the time of transfer	Embryo ploidy status	Timing of progesterone measurement	Progesterone cutoff values (ng/mL)	Intra-/ inter-assay variability range	Outcomes	Main findings	Included in meta-analysis
														.08) OPR was lower in women with high progesterone level (>14.2 ng/mL) vs. women with intermediate progesterone levels (crude OR 0.56, 95% CI 0.32 to 0.98, *P* .04) The rate of early pregnancy loss was comparable across all three groups (*P* .57)	
González-Foruria et al. (27)	Retrospective cohort (Mar 2016 to Feb 2018)	Autologous	Age <45 years; SET	Donor cycles; DET; endometrium <5mm after estradiol	HRT-FET	685	PV micronized capsules 200 mg TDS; continued until 10 weeks of gestation	Day 5/6 blastocysts	Unstated	Day before FET (Day 5 of progesterone administration) 1–18 h after progesterone administration	None identified	2.4%–11.9%	Live birth	Linear positive correlation between serum progesterone level and LBR No optimal category of progesterone levels associated with higher LBR	No
Commissaire et al. (40)	Retrospective cohort with case-control analysis (Jun 2016 to Jul 2017)	Unspecified	Age 18–43 years; BMI <32 kg/m^2	NC-FET	HRT-FET	130	PV micronized capsules 200 mg mane and 400 mg nocte; continued until 12 weeks of gestation	Cleavage stage (until Apr 2016); blastocysts (after Apr 2016)	Unstated	Day of pregnancy test: 10 or 12 days after FET, depending on the embryo stage at transfer (Day 4–6 of progesterone administration) Repeated 48 h and 96 h after pregnancy test Time from progesterone administration not specified	None identified	Unstated	Pregnancy (serum hCG >100 IU/mL) Clinical pregnancy Miscarriage Ongoing pregnancy	No linear correlation identified between progesterone levels and treatment outcome, although serum progesterone level on the day of pregnancy test was higher in women with ongoing pregnancy vs. those with miscarriage (12.4 ng/mL, IQR 7.5 to 14.6 ng/mL, vs. 8.2 ng/mL, IQR 5.9 to 13.8 respectively, *P* .048)	No - case-control analysis Investigators contacted—did not identify direct link between serum progesterone level and outcomes
Gaggiotti-Marre et al. (52)	Retrospective cohort (Jan 2016 to Jan 2019)	Autologous	Regular menstrual cycles	Uterine pathology; mosaic ET; oocyte recipient cycles	NC-FET	294	NA	Blastocysts	Unstated	Day before FET (6 days after LH surge)	<10 (n 109); ≥10 (n 185)	1.2%–23.1%	Clinical pregnancy Miscarriage Live birth	Progesterone level ≥10 ng/mL associated with increased LBR	Yes

Melo. Serum progesterone in FET cycles. Fertil Steril 2021.

TABLE 1

Continued.

Source	Study design and duration	Autologous/ donor cycles	Inclusion criteria	Exclusion criteria	HRT-FET/ NC-FET	Number of FET cycles analyzed	Progesterone route of administration and dose	Embryo stage at the time of transfer	Embryo ploidy status	Timing of progesterone measurement	Progesterone cutoff values (ng/mL)	Intra-/ inter-assay variability range	Outcomes	Main findings	Included in meta-analysis
														(41.1% vs. 25.7%, RD 15.4%, 95% CI 5% to 26%) and higher CPR (48.6% vs. 33.0%, RD 15.6%, 95% CI 4% to 27%) MR was similar between the two groups (P>.05)	
Shiba et al. (47)	Nested cohort analysis of prospective randomized controlled trial (Dec 2016 to Dec 2017)	Unspecified	No restrictions	Contraindications to progesterone formulation	HRT-FET	235	PV micronized suppositories administered 100 mg TDS; 200 mg TDS; 400 mg BD, or 90 mg OD; duration of progesterone not stated	Cleavage stage (n 111) or blastocysts (n 124)	Unstated	Day of FET (Day 3–6 of progesterone administration according to stage of embryo development at freezing) 4 h after progesterone administration	<7.8 (n 59); 7.8–10.8 (n 59); 10.8–13.7 (n 59); >13.7 (n 58)	Unstated	Clinical pregnancy Miscarriage Live birth	No statistically significant differences between the four progesterone categories for the outcomes of CPR, LBR, and MR	Yes
Ramos et al. (41)	Retrospective cohort (Feb 2019 to Dec 2019)	Autologous	Age 18–42 years; BMI 18–30 kg/m^2; morphologically normal uterus on hystero sonography and/or hysteroscopy	E2 priming >28 days; history of RPL; uterine pathology; ET <7mm after E2	HRT-FET	320	PV micronized capsules 800 mg/ day and SC 25 mg/day; continued until 8 weeks of gestation	Blastocysts	Unstated	1 or 2 days before FET (Day 4 or 5 of progesterone administration) Time from progesterone administration not specified	<14.53 (n 79); 14.53–21.94 (n 81); 21.95–45.32 (n 80); >45.33 (n 80)	Unstated	Implantation rate Clinical pregnancy Miscarriage Ongoing pregnancy	No statistically significant differences between the four serum progesterone categories for the outcomes of CPR, OPR, and MR When analyzing "high" vs. "low" progesterone level according to the median value of 21.94 ng/mL, MR was lower in the high progesterone group (12.3% vs. 27.6%, respectively, P< .05)	Yes
Liu and Wu (53)	Retrospective cohort (Jan 2015 to Dec 2018)	Autologous	Age <48 years; first FET cycle	Donor cycles; oocyte cryopreservation	HRT-FET	856 (262 suitable for meta-analysis)	PO dydrogesterone 30 mg/day with either IM progesterone 60 mg/day or PV micronized progesterone gel 8%, 90 mg/day; continued until	Day 2/3 cleavage stage	Unstated	Day of pregnancy test: 14 days after FET Time from progesterone administration not specified	≤13.15 (n 131); >13.15 (n 131)	Unstated	Clinical pregnancy Live birth	When analyzing "high" vs. "low" progesterone level according to the median value of 13.15 ng/mL in women who received IM progesterone for LPS, the LBR was increased in the	Yes—only women who had IM progesterone

Melo. Serum progesterone in FET cycles. Fertil Steril 2021.

TABLE 1

Continued.

Source	Study design and duration	Autologous/ donor cycles	Inclusion criteria	Exclusion criteria	HRT-FET/ NC-FET	Number of FET cycles analyzed	Progesterone route of administration and dose	Embryo stage at the time of transfer	Embryo ploidy status	Timing of progesterone measurement	Progesterone cutoff values (ng/mL)	Intra-/ inter-assay variability range	Outcomes	Main findings	Included in meta-analysis
							12 weeks of gestation							high progesterone group (45.0% vs. 32.8%, respectively, adjusted OR 1.68, 95% CI 1.002 to 2.85, *P* .049) In addition, CPR increased in the high progesterone group (54.9% vs. 41.98, respectively, adjusted OR 1.67, 95% CI 1.005 to 2.774, *P* .048)	
Al Jarrah et al. (48)	Prospective cohort (Oct 2019 to Apr 2020)	Unspecified	Age 20–40 years; BMI 19–35 kg/m^2; morphologically normal uterus; normal hystero sonography	RIF; uterine pathology; adnexal pathology (e.g., hydrosalpinx, ovarian cyst); ET <7 mm after E2	HRT-FET	60	PV micronized progesterone pessaries 400 mg BD ± IM progesterone 50 mg OD; continued until 10–12 weeks of gestation	Cleavage stage	Unstated	Day of FET (Day 4 of progesterone administration) >8 h after progesterone administration	None identified	Unstated	Clinical pregnancy Miscarriage Ongoing pregnancy	No correlation identified between progesterone levels and treatment outcome	No Case-control analysis Progesterone levels were not predictive of pregnancy outcomes
Alyasin et al. (49)	Prospective cohort (Feb 2019 to Jan 2020)	Autologous	Age <40 years; BMI <30 kg/m^2; first or second FET cycle; top-quality blastocysts	Donor cycles; RIF/RM; severe male factor; uterine pathology; adnexal pathology (e.g., hydrosalpinx)	HRT-FET	258	PV micronized suppositories 400 mg OD, increased to TDS over the first three days of supple mentation, and IM 25–50 mg/ day; continued until 10 weeks of gestation	Blastocysts	Unstated	Day of FET (Day 5 of progesterone administration) 4–6 h after progesterone administration	<19.0 (n 64); 19.0–29.0 (n 65); 29.0–49.0 (n 65); >49.0 (n 64)	<10%	Clinical pregnancy Miscarriage Live birth	CPR and LBR were lower in women with progesterone level in the fourth quartile (>49 ng/ mL) when compared with participants with progesterone level in the three lower quartiles (≤49 ng/mL, CPR 18.8% vs. 41.2%, respectively, *P* .002; LBR 17.2% vs. 39.7%, respectively, *P* .002) MR was similar between the different groups (*P*>.05) ROC analysis showed that the optimum level of serum progesterone	Yes

Melo. Serum progesterone in FET cycles. Fertil Steril 2021.

TABLE 1

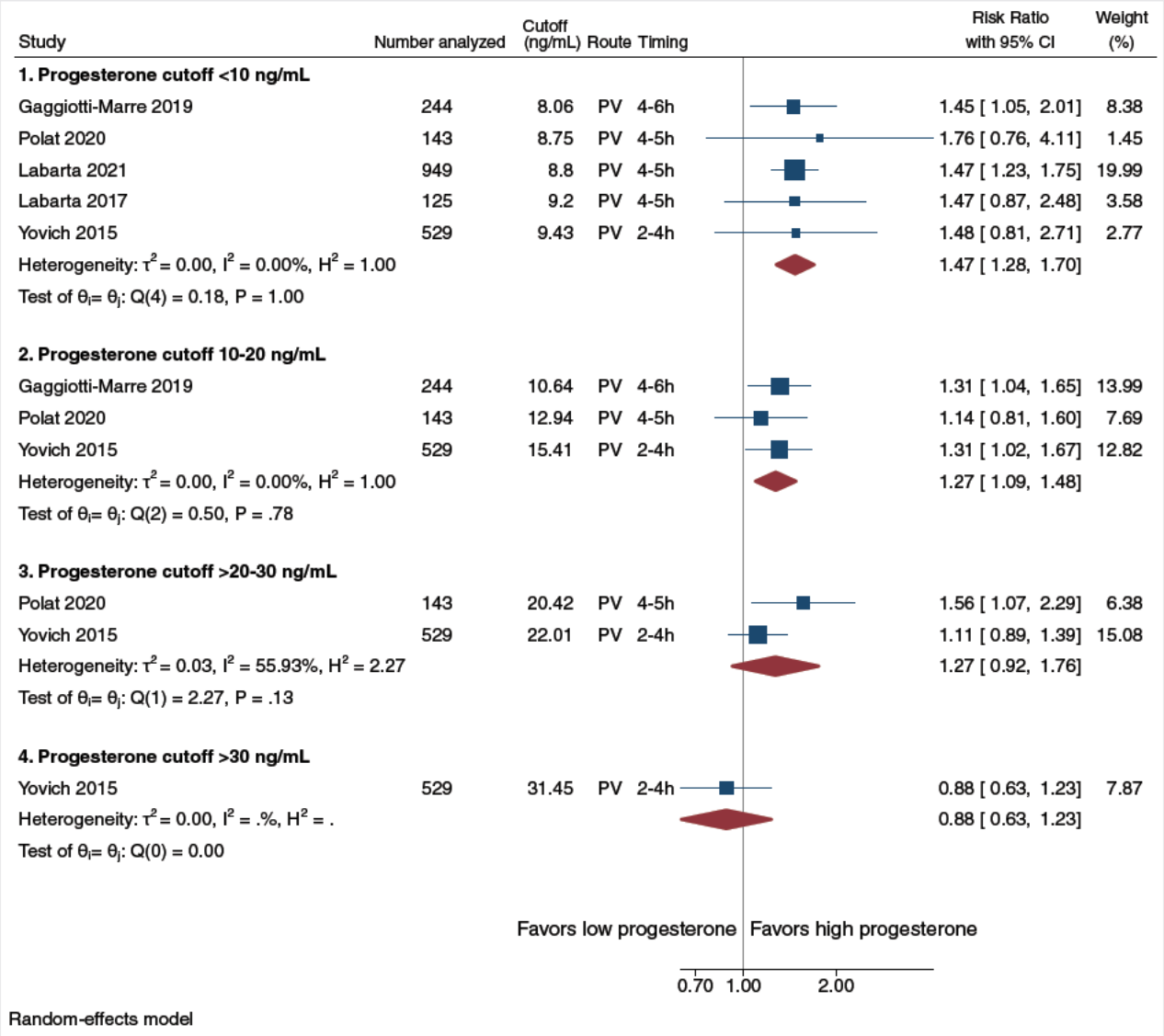
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Source	Study design and duration	Autologous/ donor cycles	Inclusion criteria	Exclusion criteria	HRT-FET/ NC-FET	Number of FET cycles analyzed	Progesterone route of administration and dose	Embryo stage at the time of transfer	Embryo ploidy status	Timing of progesterone measurement	Progesterone cutoff values (ng/mL)	Intra-/ inter-assay variability range	Outcomes	Main findings	Included in meta-analysis
														was 32.5 ng/mL, with 70% sensitivity and 50% specificity for LBR	
Labarta et al. (28)	Prospective cohort (Sep 2017 to Nov 2018)	Mixed	Age ≤50 years; triple layer endometrium and thickness ≥6.5 mm after E2; day 5/6 blastocysts	Uterine pathology; adnexal pathology (e.g., hydrosalpinx)	HRT-FET	949 HRT-FET (Total study sample included additional 201 fresh donor cycles, total n 1,150)	PV micronized capsules 400 mg BD Continued until 12 weeks of gestation	Day 5/6 blastocysts	Unstated	Day of FET (Day 6 of progesterone administration) 4–5 h after progesterone administration	Total cohort (HRT-FET plus fresh donor cycles) >8.8 (n 806); ≤8.8 (n 344); HRT-FET subgroup: >8.8 (n 624); ≤8.8 (n 303)	1.2%–23.1%	Clinical pregnancy Miscarriage Ongoing pregnancy Live birth	Analysis of the total cohort (HRT-FET plus fresh donor cycles) showed that women with low progesterone level (≤8.8 ng/mL) had lower OPR than those with progesterone level >8.8 ng/mL (36.6% vs. 54.4%, respectively, *P*< .001), as well as lower LBR (35.5% vs. 52.0%, respectively, *P*< .001) and higher MR (23% vs. 13.5%, respectively, *P* .006). Analysis of the HRT-FET subgroup showed that women with progesterone level ≤8.8 ng/mL had lower LBR (34% vs. 49.8%, *P*< .001), lower CPR (45.4% vs. 59.6%, *P*< .001) and higher MR (35.8% vs. 22.3%, *P*< .001)	Yes

Note: BD twice daily; BMI body mass index; CI confidence interval; CPR clinical pregnancy rate; DET double embryo transfer; E2 estradiol; ET endometrial thickness; FET frozen embryo transfer; hCG human chorionic gonadotropin; HRT hormone replacement therapy; HRT-FET hormone replacement therapy frozen embryo transfer; IM intramuscular administration; IQR interquartile range; LBR live birth rate; LH luteinizing hormone; LPS luteal phase support; MR miscarriage rate; NA not applicable; NC-FET natural cycle FET; NS non-significant; OD once daily; OPR ongoing pregnancy rate; OR odds ratio; PGT-A/MD/SR preimplantation genetic testing for aneuploidies / monogenic disorders / structural rearrangements; PO oral administration; PR rectal administration; PV vaginal administration; RD risk difference; RIF recurrent implantation failure; RM recurrent miscarriage; ROC receiver operating characteristic curve; RPL recurrent pregnancy loss; SC subcutaneous administration; SET single-embryo transfer; TDS three times daily.

Melo. Serum progesterone in FET cycles. Fertil Steril 2021.

FIGURE 1



Forest plot describing the association between different threshold categories of serum progesterone level and ongoing pregnancy or live birth rates for women undergoing frozen embryo transfer cycles using blastocyst embryos and PV progesterone only. CI confidence interval; PV vaginal route.

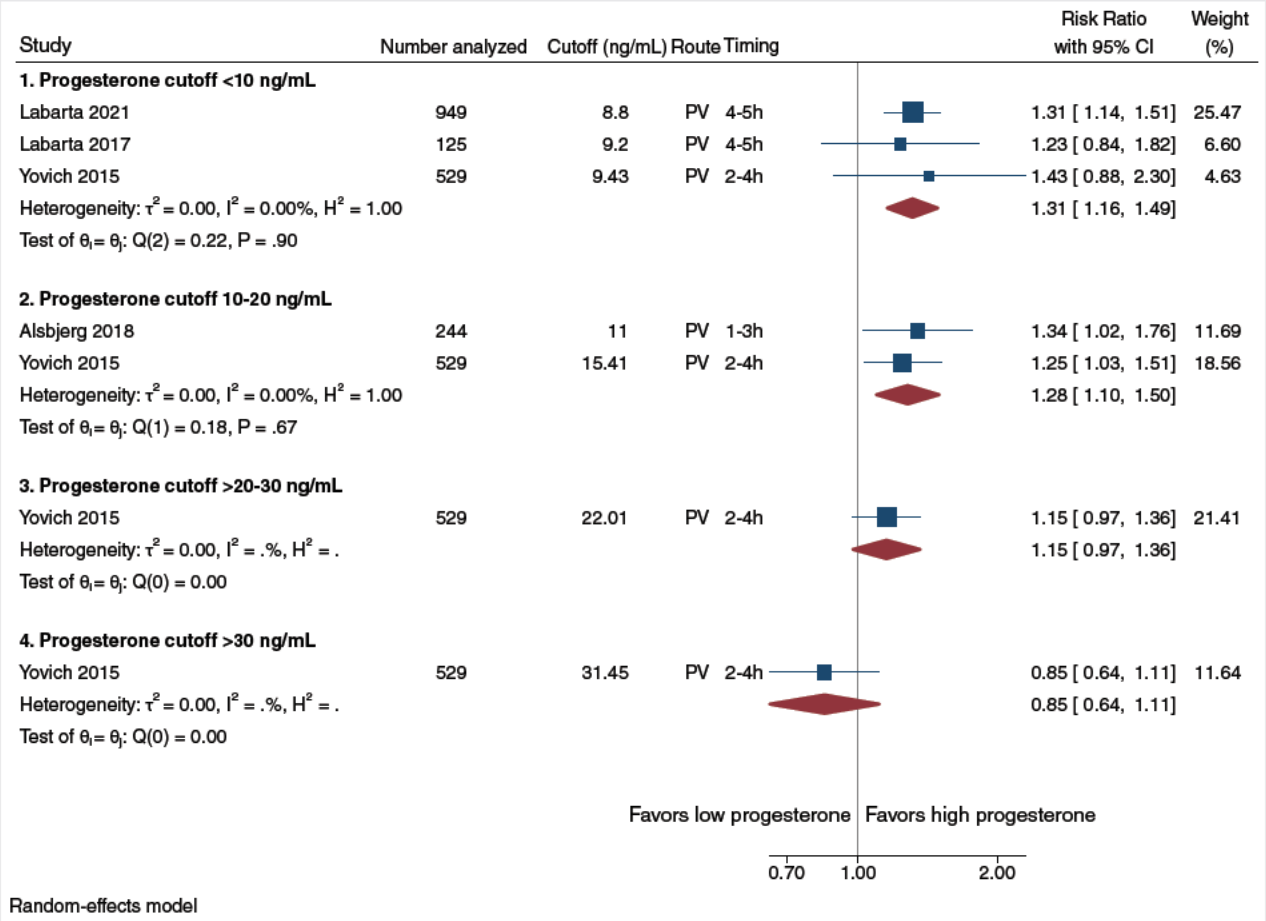
Melo. Serum progesterone in FET cycles. Fertil Steril 2021.

manuscripts (44, 52), and >28 weeks in the study by Liu and Wu (53), whereas the remaining 7 publications did not specify a gestational age for live birth (27, 28, 31, 46, 47, 49, 50). Eleven studies reported on ongoing pregnancy, defined by most as the presence of fetal heart activity at ≥12 weeks' gestation (17, 26, 28, 40–42, 45, 46, 48), with one study using the threshold of 16 weeks (43) and another leaving the threshold unspecified (31). Seventeen studies reported on clinical pregnancy, defined as the presence of a gestational sac on ultrasound in 10 studies (15, 26, 28, 32, 42, 43, 47, 51–53), whereas the remaining 7 publications defined clinical pregnancy as the presence of an intrauterine gestational sac with visible fetal heart activity (17, 31, 40, 41, 45, 48, 49). Finally, seventeen studies reported on miscarriage, of which eleven used thresholds between 6 and 12 weeks' gestation (17, 26, 28, 31, 40, 42–45, 48, 51); one used a cutoff of 20 weeks (49); another study used a threshold of 22 weeks (52); and four studies did not specify gestational ages for miscarriage (41, 46, 47, 50). No studies reported on adverse events attributable to progesterone.

Quantitative Synthesis of Serum Progesterone Level Effects

We performed meta-analyses of studies reporting on OPR or LBR and CPR per cycle and MR per pregnancy. We grouped the study results according to different threshold categories

FIGURE 2



Forest plot describing the association between different threshold categories of serum progesterone level and clinical pregnancy rates for women undergoing frozen embryo transfer cycles using blastocyst embryos and PV progesterone only. CI confidence interval; PV vaginal route.

Melo. Serum progesterone in FET cycles. Fertil Steril 2021.

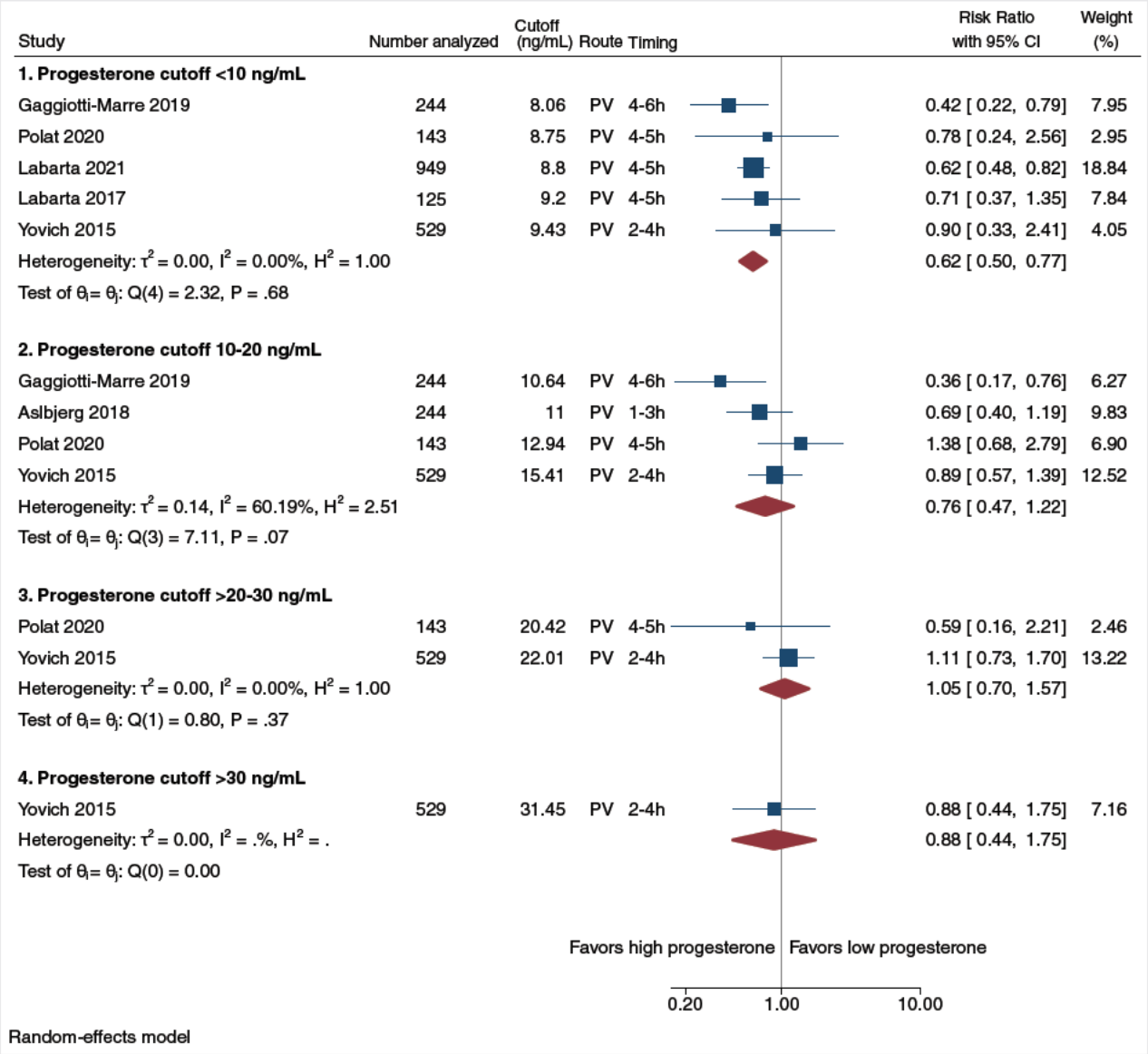
used by the investigators to present outcome data. Within each threshold category (<10, 10–20, >20–30, and >30 ng/mL), outcome data were presented for women with "high" (i.e., above that particular cutoff) and "low" (i.e., below the cutoff) progesterone level. Although it was possible to conduct meta-analyses of studies using PV-only progesterone and blastocyst embryos, there were an insufficient number of studies to perform meta-analyses for cleavage-stage embryos and for the IM, PO, PR, and SC routes of progesterone administration.

Progesterone threshold category <10 ng/mL. Among studies using solely PV progesterone and blastocyst embryos, meta-analysis of the outcome data for cutoff values <10 ng/mL showed that a serum progesterone level higher than the specified threshold was associated with increased OPR or LBR (RR 1.47, 95% CI 1.28 to 1.70; five studies; n = 1,990; I^2 = 0%) (Fig. 1), increased CPR (RR 1.31, 95% CI 1.16 to 1.49; three studies; n = 1,603; I^2 = 0%) (Fig. 2), and reduced MR (RR 0.62, 95% CI 0.50 to 0.77; five studies; n = 1,990; I^2 = 0%) (Fig. 3). The aforementioned sensitivity analyses did not change the conclusions (Supplemental Fig. 2, Supplemental Fig. 3, and Supplemental Fig. 4).

The pooled aOR for studies using PV-only progesterone showed that a lower serum progesterone level was associated with a reduction in OPR or LBR (aOR 0.48, 95% CI 0.35 to 0.62; two studies; n = 1,074; I^2 = 30.9%) (Supplemental Fig. 5). A meta-analysis of the adjusted effect estimates was not possible for CPR and MR within this threshold category because of insufficient data.

Progesterone threshold category 10–20 ng/mL. For studies using PV-only progesterone and blastocyst embryos in which the serum progesterone level cutoff values ranged between 10 and 20 ng/mL, the primary analysis showed that a higher progesterone level was associated with increased OPR or LBR (RR 1.27, 95% CI 1.09 to 1.48; three studies; n = 916; I^2 = 0%) (Fig. 1) and improved CPR (RR 1.28, 95% CI 1.10 to 1.50; two studies; n = 773; I^2 = 0%). However, sensitivity analyses including all studies, regardless of the progesterone route, type of FET, or risk of bias, showed uncertainty about whether higher progesterone level was associated with increased OPR or

FIGURE 3



Forest plot describing the association between different threshold categories of serum progesterone level and miscarriage rates for women undergoing frozen embryo transfer cycles using blastocyst embryos and PV progesterone only. CI confidence interval; PV vaginal route.

Melo. Serum progesterone in FET cycles. Fertil Steril 2021.

LBR (RR 1.19, 95% CI 0.98 to 1.45; 11 studies; n = 4,436; I^2 = 77.6%) (Supplemental Fig. 2) and higher CPR (RR 1.21, 95% CI 0.99 to 1.47; 11 studies; n = 4,252; I^2 = 77.5%) (Supplemental Fig. 3).

In addition, the evidence was uncertain about whether women with progesterone levels above the specified threshold within this category experienced fewer miscarriages than those with lower progesterone levels (RR 0.76, 95% CI 0.47 to 1.22; four studies; n = 1,160; I^2 = 60.2%) (Fig. 3). The sensitivity analyses for MR did not change the conclusions (Supplemental Fig. 4).

The pooled aOR for studies using PV-only progesterone showed that a lower serum progesterone level was associated with a reduction in OPR or LBR (aOR 0.37, 95% CI 0.27 to 0.47; three studies; n = 2,068; I^2 = 43.6%) (Supplemental Fig. 5) and CPR (aOR 0.45, 95% CI 0.32 to 0.57; two studies; n = 1,824; I^2 = 0%) (Supplemental Fig. 6), whereas there was uncertainty about whether a lower progesterone level was associated with an increased risk of miscarriage (aOR 1.64, 95% CI 0.73 to 2.56; three studies; n = 2,068; I^2 = 36.9%) (Supplemental Fig. 7).

Progesterone threshold category >20–30 ng/mL. When pooling data from studies using exclusively PV progesterone and blastocysts in which the results were presented for progesterone thresholds between >20 and 30 ng/mL, the serum

progesterone level measurements did not confidently correlate with OPR or LBR (RR 1.27, 95% CI 0.92 to 1.76; two studies; n = 672; I^2 = 55.9%) (Fig. 1) and MR (RR 1.05, 95% CI 0.70 to 1.57; two studies; n = 672; I^2 = 0%) (Fig. 3). Only one study in the PV progesterone group reported within this threshold for CPR, and its findings were uncertain (RR 1.15, 95% CI 0.97 to 1.36; n = 529). The sensitivity analyses did not materially change the conclusions (Supplemental Fig. 2, Supplemental Fig. 3, and Supplemental Fig. 4). A meta-analysis of the adjusted effect estimates was not possible for OPR or LBR, CPR, and MR within this threshold category because of insufficient data.

Progesterone threshold category >30 ng/mL. For progesterone thresholds >30 ng/mL, only one study using blastocysts and the PV route of administration reported on OPR or LBR, CPR, and MR, with uncertain findings for all three outcomes (Fig. 1, Fig. 2, and Fig. 3). The aforementioned sensitivity analyses did not change the effect size of the progesterone levels within this category (Supplemental Fig. 2, Supplemental Fig. 3, and Supplemental Fig. 4). A meta-analysis of adjusted effect estimates was not possible for OPR or LBR, CPR, and MR within this threshold category because of insufficient data.

Additional Analyses

There were an insufficient number of studies administering IM, PO, PR, or SC progesterone for additional analyses according to the administration route. Furthermore, only three studies analyzed cycles using exclusively euploid embryos, thus precluding sensitivity analyses according to the embryo ploidy status.

Risk of Bias across Studies

Most of the included studies were deemed to be at a low risk of bias (15, 17, 26–28, 31, 40, 42, 43, 45–49, 51–53), whereas four publications were judged to be at a moderate risk of bias (32, 41, 44, 50) because of a lack of data on whether participants within the different serum progesterone range groups were comparable in baseline demographic characteristics such as age and BMI (Supplemental Table 3).

DISCUSSION

Summary of Evidence

In this systematic review and meta-analysis of 21 cohort studies, we aimed to investigate the association between the serum progesterone level around the time of FET and treatment outcomes. The primary analysis showed that for thresholds <10 ng/mL, participants with higher progesterone levels experienced more ongoing pregnancies or live births, more clinical pregnancies, and fewer miscarriages than those with serum progesterone levels lower than the specified cutoff. This was corroborated by our sensitivity analyses. For progesterone thresholds ≥10 ng/mL, however, there was uncertainty in whether a higher progesterone level was associated with better treatment outcomes, owing to significant inter-study heterogeneity, a paucity of prospective data, and wide CIs around pooled effect estimates.

Among the included studies, progesterone was administered via different routes and in varying doses. To date, there has been no consensus on the best form of LPS in frozen embryo cycles because of a lack of robustly designed randomized trials. In a seminal study by Miles et al. (54) that included 20 ovulatory women, the investigators compared the pharmacokinetic profile of micronized progesterone administered vaginally vs. intramuscularly. Although the serum concentrations of progesterone were more than twice as high after IM administration, women assigned to the PV route had a mean endometrial progesterone concentration nearly eight times higher than that of the IM group. Importantly, however, the study participants did not have a diagnosis of infertility, and reproductive outcomes were not assessed. In a subsequent randomized trial, Lightman et al. (55) compared micronized progesterone PV (200 mg three times daily) with IM progesterone (100 mg once daily) in 354 women undergoing HRT-FET cycles. The serum progesterone level on the day of the pregnancy test was more than double in the IM progesterone group, yet crucially did not result in higher CPR. These findings support the hypothesis that the endometrial rather than the serum progesterone level is more important in determining treatment success in FET cycles. This may additionally reflect the phenomenon of first uterine pass, whereby a targeted delivery of PV progesterone to the uterus enhances the local endocrine milieu and hence facilitates implantation and pregnancy success (56). Overall, however, studies comparing different routes and regimens of LPS in FET have failed to categorically identify a formulation with superior results (42, 47, 57–61).

Despite the lack of evidence attesting to superior efficacy, the use of micronized PV progesterone for LPS in ART has become widespread in recent decades. There were originally concerns about reduced bioavailability of natural progesterone because of its large molecular size, but in its micronized form, progesterone has since been shown to be easily absorbed by the vaginal and intestinal mucosa (62, 63). Furthermore, gel-based formulations containing micronized progesterone exhibit a sustained-release mechanism that leads to steady levels of absorption over time and prevents excessive variation in serum progesterone levels (59, 60). The PV formulation is most commonly used in ART treatment across the world and is the preferred route of administration for up to one in four ART practitioners (64). In this review, most studies used PV progesterone, IM progesterone, or a combination of both routes for LPS. Although it is difficult to link the route of administration with progesterone level measurements across different studies, the analysis by Polat et al. (42) identified higher progesterone levels in the group receiving PV plus IM progesterone in comparison with levels in those assigned to PV progesterone only. However, there was no evidence that the treatment outcomes differed between the two cohorts. In addition to PV-only progesterone, we aimed to conduct meta-analyses evaluating other routes of administration. Although the number of studies using IM, PO, PR, and SC progesterone were insufficient for performance of grouped analyses, we carried out sensitivity analyses including all studies, regardless of the route of administration and stage of embryo development. The

primary analysis of studies using PV-only progesterone showed that higher circulating levels were associated with increased OPR or LBR for the threshold categories of <10 ng/mL and 10–20 ng/mL, yet our sensitivity analyses including all studies showed that this was no longer the case for progesterone thresholds ranging between 10 and 20 ng/mL. These data strengthen the argument that although systemic routes of administration such as SC or IM may result in higher circulating progesterone levels, this does not necessarily reflect the amount that actually reaches the endometrium, which may be lower, thus explaining the dilution in effect size observed in the sensitivity analysis for the outcome of OPR or LBR.

There was variation across the studies in the timing of the progesterone level measurement, although those assessing blastocyst transfers undertook venepuncture at least 4 days after the onset of LPS. The pharmacokinetics of different progesterone formulations have been the subject of much research. For example, there have been concerns regarding the low bioavailability of progesterone when administered orally because of the effect of food on intestinal absorption and the phenomenon of first hepatic pass leading to the rapid metabolization and excretion of progesterone metabolites (65). In the past decade, however, dydrogesterone, a synthetic progestogen, has been increasingly used in ART because of its improved bioavailability, safety, and convenience of use (66). When progesterone is administered vaginally or intramuscularly, a steady state in the serum concentration is usually achieved within 24–48 hours (62, 67, 68). In the case of SC progesterone, the time to steady-state concentrations ranges between 48 and 72 hours (69). Therefore, in this review, it is reasonable to postulate that serum progesterone level measurements in all studies evaluating HRT-FET provided a reliable estimate of the steady state concentrations and were thus reflective of the circulating progesterone level at the time of embryo transfer. In addition, existing evidence suggests that serum progesterone levels remain >10 ng/mL for >18 hours after PV administration (27). Our primary analysis included only studies whose dose-to-measurement interval ranged between one and six hours and are therefore likely to accurately reflect the association between the serum progesterone level and FET treatment outcomes in this cohort of patients.

Our results confidently identified that for cutoffs <10 ng/mL, higher progesterone levels were on average associated with better treatment outcomes. However, as the threshold values increased, there was an overall shift toward the line of no effect. For the highest cutoff levels (>30 ng/mL), it was in fact unclear whether progesterone might even be detrimental to OPR and LBR (Fig. 1, Supplemental Fig. 2). It is therefore possible that a minimally important level of serum progesterone is required to ensure sufficient binding to the endometrial progesterone receptors and facilitate their secretory activity. Above this minimum threshold, however, the data suggest that treatment outcomes may not be optimized when higher circulating levels of progesterone are identified. Although mechanistic studies investigating the pharmacodynamics of progesterone receptors in the uterus of women undergoing ART are scarce, existing evidence from humans and other mammals indicates that endometrial progesterone receptors undergo saturation at or below physiological concentrations of endogenous progesterone (70, 71). Furthermore, adding progesterone to endometrial samples showed that specific binding was saturable above a threshold of approximately 3.14 ng/mL (70, 72), suggesting that beyond that level further progesterone may not enhance the secretory activity of the endometrium.

Although it may be difficult to extrapolate in vitro data to clinical practice, a recent study by Deng et al. (73) has added strength to the hypothesis of progesterone receptor saturation. The investigators demonstrated that in 726 women with threatened miscarriage in the first trimester of naturally conceived pregnancies, the risk of pregnancy loss decreased incrementally as the serum progesterone levels rose, but only up to a concentration of 28.5 ng/mL. Above this value, the risk of miscarriage was no longer associated with circulating progesterone levels (73). Although progesterone in its natural and micronized forms has a proven safety record in pregnancy (74, 75), studies in mammals have indicated that excessive progesterone may impair implantation and decidualization (76). There is hence a need for additional data investigating the effect of higher levels of circulating progesterone on FET outcomes.

Crucially, it remains uncertain whether providing additional LPS to women with low serum progesterone levels improves outcomes in FET. Cédrin-Durnerin et al. (77) conducted a retrospective analysis of 227 FET cycles in which women received a total daily dose of 600 mg of PV micronized progesterone for endometrial preparation. Although the dose of progesterone was increased to 800 mg daily in participants whose serum progesterone level was <10 ng/mL on the day of FET, these women still experienced fewer live births than those with a progesterone level ≥10 ng/mL. In a subsequent retrospective study, Volovsky et al. (78) analyzed 2,010 FET cycles in which women whose serum progesterone on the day of transfer was <8.0 ng/mL received additional supplementation. In contrast to Cédrin-Durnerin et al. (77), Volovsky et al. (78) observed no differences between CPR and LBR in women with serum progesterone level <10 ng/mL and rates in those in whom the progesterone level was ≥10 ng/mL, suggesting that additional LPS may have led to luteal rescue. More recently, Álvarez et al. (30) published a nonrandomized prospective study in which women with serum progesterone level <10.6 ng/mL on the day before FET received additional SC progesterone supplementation and experienced similar outcomes to those of participants whose serum progesterone level was >10.6 ng/mL. Importantly, this study was restricted to euploid-only cycles, thus eliminating the contribution of aneuploidy to miscarriage rates in this cohort. High-quality randomized interventional data are needed to further inform the preceding findings by ascertaining whether women with low progesterone level (<10 ng/mL) who receive additional LPS (for example, by adding a second route of administration) experience noninferior outcomes to those of women with higher progesterone levels.

Most studies included in this review stated that LPS was continued at least until the day of the pregnancy test, with

the exception of four publications in which the duration of LPS was not stated (17, 43, 46, 50) and one study in which women underwent NC-FET without LPS (27). In natural conception, the corpus luteum is the main source of progesterone from ovulation until approximately 7–8 weeks of gestation, when the luteoplacental shift occurs and endogenous steroid synthesis continues predominantly in the placenta (79). Because of the luteal phase deficiency phenomenon in fresh IVF cycles, it has been recommended that exogenous LPS should be undertaken until at least the day of the pregnancy test (80), although an international survey of >1,000 clinicians showed that worldwide most practitioners continue LPS until 12 weeks (64). However, a recent systematic review identified no difference in LBR, OPR, or MR between women who ceased progesterone early (weeks 4 to 7) and those who discontinued it later on in the first trimester (up to 12 weeks) (81). Fresh cycle data are nonetheless difficult to extrapolate to HRT-FET treatment, because the lack of a corpus luteum in the latter results in diminished levels of endogenous progesterone. It is possible that this may affect implantation and impact on the LPS requirements in FET (82). Furthermore, it has recently been suggested that vasoactive molecules produced by the corpus luteum, such as relaxin and vascular endothelial growth factor, play a key role in facilitating initial placentation, and that their absence may contribute to higher rates of hypertensive disorders observed in pregnancies resulting from HRT-FET treatment (83, 84).

Strengths and Limitations

The findings of this systematic review are strengthened by the large number of studies analyzing progesterone levels within different threshold categories, which allowed for meta-analyses for all outcomes of interest. We conducted our primary analyses according to the progesterone administration route and embryo development stage, therefore significantly reducing clinical heterogeneity. There were an insufficient number of studies evaluating euploid-only FET cycles, however, and we were therefore unable to conduct sensitivity analyses adjusting for ploidy status, a crucial determinant of pregnancy success. There is a need for additional prospective data evaluating how the serum progesterone level correlates with FET outcomes in the absence of embryonic aneuploidy.

In addition to the retrospective nature of most of the included studies, there was a significant degree of variation in PV progesterone formulations, doses, timing of administration, and serum levels found to be associated with treatment outcomes. Because of the wide range of serum progesterone level measurements reported in relation to pregnancy outcomes, we opted to group the various cutoffs by regular 10 ng/mL intervals. This classification, although arbitrary, allowed for meta-analyses of studies reporting on similar ranges of serum progesterone level. For the primary analyses, most of the cutoffs in each threshold category were in fact within 5 ng/mL intervals, hence reducing heterogeneity.

There were multiple coefficients of variation reported for different study assays in this review, ranging between 1.2% and 23.1%. This may have affected the precision and reproducibility of the included manuscripts, and crucially it may have skewed the cutoff levels reported as significant by different studies, thus potentially impacting on the real-life applicability of our findings. Further, it was not possible to conduct separate meta-analyses evaluating non-PV administration routes (IM, PO, PR, and SC) or for NC-FET, although these were included in the sensitivity analyses that corroborated our primary findings for serum progesterone levels <10 ng/mL. For serum levels ≥10 ng/mL, however, the sensitivity analyses featured high statistical and clinical heterogeneity, thus precluding generalizable recommendations.

Finally, some of the included studies did not find a linear dichotomy whereby "high" and "low" progesterone levels inversely correlated with treatment outcomes, and reported instead on serum level measurement ranges that were associated with improved treatment success. This was further compounded by the use of midrange progesterone levels as the reference group where studies calculated adjusted effect estimates, therefore preventing their inclusion in the supplemental adjusted analyses evaluating "high" vs. "low" progesterone. We conducted exploratory analyses by comparing "high-level" vs. "mid-level" vs. "low-level" progesterone for publications that analyzed interval data, although the high degree of variation in mid-level progesterone measurements between studies represented a significant challenge and precluded informative conclusions. Future cohort studies should focus on a percentile evaluation that goes beyond the dichotomous approach. Furthermore, a collaborative effort between study investigators to undertake an individual participant data meta-analysis may help clarify the trends of the effect of serum progesterone on FET outcomes.

CONCLUSION

This systematic review suggests that there is a minimum clinically important serum luteal progesterone level of approximately 10 ng/mL associated with optimal rates of ongoing pregnancy or live birth, higher chance of clinical pregnancy and reduced risk of miscarriage in women undergoing FET treatment.

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CHAPTER 4: THE EFFECT OF FROZEN EMBRYO TRANSFER REGIMEN ON THE ASSOCIATION BETWEEN SERUM PROGESTERONE AND LIVE BIRTH: A MULTICENTRE PROSPECTIVE COHORT STUDY (PROFET)

Preamble

Chapter 3 identified an association between low serum progesterone levels and reduced live birth rates in FET cycles using vaginal progesterone for luteal phase support (LPS). Chapter 4 presents the results of the ProFET study, focusing on how other types of FET protocols (namely natural cycle FET, and FET cycles using only subcutaneous or a combination of vaginal and subcutaneous progesterone) affect the association between serum progesterone and live birth.

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Authors' contributions

Dr Pedro Melo led all stages of the study, including conception, design, protocol writing, ethics approval, sponsorship, study implementation, data collection and analysis, and manuscript drafting. All other contributions have been acknowledged in the manuscript.

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ORIGINAL ARTICLE

The effect of frozen embryo transfer regimen on the association between serum progesterone and live birth: a multicentre prospective cohort study (ProFET)

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STUDY QUESTION: What is the association between serum progesterone levels on the day of frozen embryo transfer (FET) and the probability of live birth in women undergoing different FET regimens?

SUMMARY ANSWER: Overall, serum progesterone levels <7.8 ng/ml were associated with reduced odds of live birth, although the association between serum progesterone levels and the probability of live birth appeared to vary according to the route of progesterone administration.

WHAT IS KNOWN ALREADY: Progesterone is essential for pregnancy success. A recent systematic review showed that in FET cycles using vaginal progesterone for endometrial preparation, lower serum progesterone levels (<10 ng/ml) were associated with a reduction in live birth rates and higher chance of miscarriage. However, there was uncertainty about the association between serum progesterone levels and treatment outcomes in natural cycle FET (NC FET) and HRT FET using non vaginal routes of progesterone administration.

STUDY DESIGN, SIZE, DURATION: This was a multicentre (n = 8) prospective cohort study conducted in the UK between January 2020 and February 2021.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We included women having NC FET or HRT FET treatment with progester one administration by any available route. Women underwent venepuncture on the day of embryo transfer. Participants and clinical personnel were blinded to the serum progesterone levels. We conducted unadjusted and multivariable logistic regression analyses to inves tigate the association between serum progesterone levels on the day of FET and treatment outcomes according to the type of cycle and route of exogenous progesterone administration. Our primary outcome was the live birth rate per participant.

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MAIN RESULTS AND THE ROLE OF CHANCE: We studied a total of 402 women. The mean (SD) serum progesterone level was 14.9 (7.5) ng/ml. Overall, the mean adjusted probability of live birth increased non linearly from 37.6% (95% CI 26.3 48.9%) to 45.5% (95% CI 32.1 58.9%) as serum progesterone rose between the 10th (7.8 ng/ml) and 90th (24.0 ng/ml) centiles. In comparison to partici pants whose serum progesterone level was ≥7.8 ng/ml, those with lower progesterone (<7.8 ng/ml, 10th centile) experienced fewer live births (28.2% versus 40.0%, adjusted odds ratio [aOR] 0.41, 95% CI 0.18 0.91, $P = 0.028$), lower odds of clinical pregnancy (30.8% versus 45.1%, aOR 0.36, 95% CI 0.16 0.79, $P = 0.011$) and a trend towards increased odds of miscarriage (42.1% versus 28.7%, aOR 2.58, 95% CI 0.88 7.62, $P = 0.086$). In women receiving vaginal progesterone, the mean adjusted probability of live birth increased as serum proges terone levels rose, whereas women having exclusively subcutaneous progesterone experienced a reduction in the mean probability of live birth as progesterone levels rose beyond 16.3 ng/ml. The combination of vaginal and subcutaneous routes appeared to exert little impact upon the mean probability of live birth in relation to serum progesterone levels.

LIMITATIONS, REASONS FOR CAUTION: The final sample size was smaller than originally planned, although our study was ade quately powered to confidently identify a difference in live birth between optimal and inadequate progesterone levels. Furthermore, our cohort did not include women receiving oral or rectal progestogens.

WIDER IMPLICATIONS OF THE FINDINGS: Our results corroborate existing evidence suggesting that lower serum progesterone levels hinder FET success. However, the relationship between serum progesterone and the probability of live birth appears to be non linear in women receiving exclusively subcutaneous progesterone, suggesting that in this subgroup of women, high serum progesterone may also be detrimental to treatment success.

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Key words: progesterone / frozen embryo transfer / luteal phase support / live birth / miscarriage

WHAT DOES THIS MEAN FOR PATIENTS?

Progesterone is a hormone produced by the corpus luteum in the ovary, after an oocyte has been released. If the oocyte is successfully fertilised by sperm, in the fallopian tube, it becomes an embryo. The actions of progesterone enable the uterus to become receptive to the embryo as it implants in the uterine lining. Without progesterone, pregnancy loss is inevitable. There has been research investigating whether blood levels of progesterone are associated with the chance of success in women having treatment with frozen embryos. Most of the existing studies are flawed because they are retrospective, relying on historical data, which may skew study findings. In addition, the available studies have focused mainly on women receiving vaginal progesterone to support the lining of the uterus once a thawed embryo has been transferred.

We performed a prospective study in eight fertility clinics in the UK. Rather than relying on historical data, we approached patients as they presented for treatment and gathered data from those who agreed to take part in our study. We collected blood from participants on the day of frozen embryo transfer and tested the progesterone level to investigate its association with treatment outcomes. We found that low progesterone blood levels (<7.8 ng/ml) were associated with reduced probability of achieving a live birth. However, the associa tion between progesterone blood levels and the probability of achieving a live birth varied depending on the route of progesterone administration. In women receiving vaginal progesterone, higher progesterone levels were associated with a gradual increase in the average probability of a live birth, whereas in women receiving only injectable progesterone, higher progesterone levels may have reduced the chance of a live birth. In participants receiving a combination of both routes (vaginal and subcutaneous injection), the probability of live birth appeared to remain stable as serum progesterone levels increased.

Introduction

The use of frozen embryo transfer (FET) treatment has become in creasingly common around the world in the past decade (Kushnir *et al.*, 2017; Centers for Disease Control and Prevention, Society for Assisted Reproductive Technology, 2018; HFEA, 2020). This stems from evidence showing that the effectiveness of FET is non inferior to that of fresh embryo transfer treatment (Shi *et al.*, 2018; Stormlund *et al.*, 2020). Furthermore, FET significantly reduces the risk of late onset ovarian hyperstimulation syndrome (OHSS), which affects up to one in three women undergoing fresh embryo transfer immediately

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after ovarian stimulation (Mourad *et al.*, 2017). Embryo cryopreservation also allows for the use of add on therapies such as preimplantation genetic testing for aneuploidy (PGT A) and the adjustment of transfer timing based on transcriptomic analysis of the endometrium (Simón *et al.*, 2020). These reasons have led some fertility clinics to adopt a universal 'freeze all' policy, facilitated by recent advances in cryopreservation and embryo culture techniques (Blockeel *et al.*, 2019).

There are different ways to prepare the endometrium for FET treatment. Embryo thawing and transfer may be undertaken in the luteal phase of a woman's natural menstrual cycle (NC FET), with or without progesterone supplementation, or following the sequential administration of HRT with exogenous oestrogen and progesterone (HRT FET) to mimic a natural uterine cycle (Labarta and Rodríguez, 2020). In FET cycles using progesterone supplementation, this can be administered via different routes, including vaginal, intramuscular, subcutaneous, rectal or oral routes, with varying pharmacokinetics. There remains debate on the route and dosage of progesterone associated with optimum treatment outcomes in FET, with recent studies yielding conflicting results (Shapiro *et al.*, 2014; Devine *et al.*, 2021; Santos Ribeiro *et al.*, 2021).

Regardless of whether progesterone is synthesised endogenously or exogenously administered, it is widely accepted that in its absence, pregnancy invariably fails (Csapo *et al.*, 1974). This has led some investigators to postulate that the level of serum progesterone around the time of FET may be associated with treatment success (Kofinas *et al.*, 2015; Yovich *et al.*, 2015; Labarta *et al.*, 2017). There is no consensus on this matter, however. Some argue that the uterine levels of progesterone are more critical to pregnancy success than serum measurements, while other researchers advocate that the systemic effects of progesterone are just as important to ensure the right immune endocrine milieu is present at the time of implantation and placentation (Shah *et al.*, 2019; Labarta *et al.*, 2021b).

There have been several studies investigating the association between serum luteal progesterone and FET outcomes. In a recent systematic review and meta analysis, we found evidence that low serum progesterone (<10 ng/ml) around the time of FET was associated with reduced odds of ongoing pregnancy or live birth, lower clinical pregnancy rates and higher risk of miscarriage (Melo *et al.*, 2021). However, our primary analyses were restricted to participants having HRT FET with vaginal progesterone only, due to a lack of data on women undergoing NC FET and HRT FET with non vaginal routes of progesterone administration. In addition, there was uncertainty about whether the odds of treatment success increased linearly as progesterone levels rose. We identified a need for prospective data analysing FET outcomes according to serum progesterone levels in a continuous fashion to account for a non linear association rather than focusing exclusively on the 'high' versus 'low' serum progesterone dichotomy. In addition, there remains a paucity of studies investigating the association between serum progesterone and treatment outcomes in women having NC FET and non vaginal routes of progesterone for luteal phase support.

Here, we present the results of the first multicentre prospective cohort study aimed at investigating the association between serum progesterone levels and the probability of live birth in women undergoing different FET regimens.

Materials and methods

Design

This was a multicentre, prospective cohort study conducted in eight CARE fertility clinics in the UK (Bath, Birmingham, Chester, London, Manchester, Northampton, Nottingham and Sheffield) between January 2020 and February 2021.

Ethics approval

The ProFET study protocol was approved by the CARE Fertility institutional review board (IRB) committee on 3 November 2019. The IRB panel members were all independent of CARE Fertility and included a university fellow, a senior clinical trials fellow and a senior research nurse. The study protocol was also approved by the medical directors of all participating clinics. We registered the study on ClinicalTrials.gov prospectively on 20 November 2019 (NCT04170517).

We obtained verbal and written consent from all participating women and kept an anonymised study log with reasons for refusal to participate. Women were able to withdraw from the study at any point.

Study population

We approached all women undergoing FET with blastocyst embryos in the participating sites. CARE Fertility policy restricts fertility treatment to women with body mass index (BMI) <35 kg/m^2. We excluded women whose clinician had planned serum progesterone testing during FET treatment (without blinding) and those undergoing endometrial receptivity array testing. We analysed only the first FET cycle conducted in each participant for the duration of the study, to allow for analyses per participant, to minimise bias resulting from non independent treatment cycles, and to avoid statistical adjustments for repeated measures in women having two or more cycles (Dias *et al.*, 2008; Higgins *et al.*, 2022).

NC-FET protocol

Women undergoing NC FET attended on Day 10 of their menstrual cycle for a transvaginal ultrasound scan (Voluson® S8, General Electrics, UK), and every two days thereafter. Once a dominant follicle measuring ≥14 mm was identified, participants began testing their urine twice daily to detect a spontaneous LH surge (Day 0). Where no LH surge was identified within 48 hr of visualisation of a dominant follicle, we repeated a transvaginal ultrasound to rule out ovulation and triggered ovulation as required with recombinant human chorionic gonadotropin (Ovitrelle® 250 µg, Merck, UK) or urinary hCG (Gonasi® 5000 international units, IBSA, UK) administered subcutaneously. Previously cryopreserved Day 5 or 6 blastocysts were thawed and transferred on Day 6 after a spontaneous LH surge, or Day 7 after hCG trigger injection. The decision to administer exogenous progesterone supplementation from the day of embryo transfer was left to the discretion of the attending clinicians and study participants. Where the local policy was to administer exogenous progesterone, this was given either as micronised progesterone vaginal capsules (Utrogestan®, Besins Healthcare, UK) or pessaries (Cyclogest®, L.D. Collins & Co., UK) 400 mg two times daily, from the day of embryo transfer. The decision on the progesterone regimen was made

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according to local protocols and/or clinician and patient preference. A urine pregnancy test was performed 16 days after embryo transfer, and pregnant women receiving progesterone supplementation continued it until 10–12 completed weeks of gestation. A transvaginal ultrasound scan was performed at ~6–7 weeks of gestation to diagnose clinical pregnancy and confirm viability.

HRT-FET protocol

In programmed FET cycles, the use of pituitary downregulation drugs was optional and varied according to local practice. Women who underwent downregulation received gonadotropin releasing hormone agonist injections (buserelin acetate, Suprecur®, Sanofi Aventis, UK) 0.5 mg once daily subcutaneously from Day 21 of the preceding menstrual cycle. We confirmed pituitary downregulation upon visualising quiescent ovaries and a thin endometrial lining (<4 mm) on transvaginal ultrasound.

Once downregulation was achieved, oestradiol valerate (Progynova®, Bayer, UK) was initiated at a dose of 2–4 mg three times daily, administered as oral tablets for at least 10 days. On Day 10 of oestradiol administration, we performed a transvaginal ultrasound scan to assess endometrial thickness (ET). In women whose ET was <9 mm, consideration was given to prolonging oral oestradiol treatment for another 4–7 days, or to adding a second route of administration, usually in the form of oestradiol transdermal patches (Evorel®, Theramex, UK) 100 µg once every 2–3 days. In participants undergoing HRT FET without pituitary downregulation, the aforementioned regimen of oestradiol valerate was commenced on Day 2 of menstruation.

Following treatment with oestradiol valerate, all women undergoing HRT FET cycles received progesterone supplementation for ~120–124 hr prior to embryo transfer (i.e. 5 completed days of progesterone supplementation before FET). Progesterone was administrated either as micronised progesterone vaginal capsules (Utrogestan®, Besins Healthcare, UK) or pessaries (Cyclogest®, L.D. Collins & Co., UK) 400 mg two to three times daily, subcutaneous injection (Lubion®, Pharmasure, UK) 25 mg twice daily, or combined vaginal progesterone 400 mg twice daily and subcutaneous injection 25 mg once daily. Treatment outcomes were assessed in the same manner as that described for the NC FET protocol.

Embryo transfer

Previously cryopreserved Day 5 or 6 blastocysts were thawed on the day of embryo transfer and kept in a single step medium (global® total®, CooperSurgical, UK). Embryo transfer was performed under transabdominal ultrasound guidance (Voluson® S8, General Electrics, UK) using a Sure Pro® or Sureview® catheter (Wallace®, CooperSurgical).

Progesterone measurement

All participating women underwent venepuncture on the day of FET, between 12:00 and 14:00 hours. In those receiving exogenous progesterone, the timing of blood sampling corresponded to ~4–6 hr after the last dose of progesterone administration. We measured serum progesterone levels in a central laboratory using a high throughput immunochemistry assay (Cobas® e801, Roche Diagnostics, Germany). The measurement interval for serum progesterone ranged between 0.06 and 60.1 ng/ml. The intra- and inter-assay coefficients of variation ranged between 1.1% and 20.7% and 3.3% and 12.4%, respectively.

Outcomes

Our primary outcome was the live birth rate per woman, defined as the birth of a live fetus at 24 or more weeks of gestation. The secondary outcomes were: the biochemical pregnancy rate per woman, defined as a positive urine or serum pregnancy test following embryo transfer; the clinical pregnancy rate per woman, defined as the presence of at least one gestational sac on transvaginal ultrasound; the implantation rate, defined as the number of gestational sacs seen on transvaginal ultrasound divided by the number of embryos transferred; the miscarriage rate per biochemical pregnancy, defined as any pregnancy lost before week 12 of gestation; and the ectopic pregnancy rate per biochemical pregnancy, defined as pregnancy outside the uterine cavity, diagnosed by ultrasound, surgical visualisation or histopathology (Zegers Hochschild *et al.*, 2017).

Follow-up

Participants were prospectively followed up until 31 December 2021, with final treatment outcome confirmed by telephone call.

Sample size

Our systematic review showed that the ongoing pregnancy or live birth rate in women with inadequate progesterone levels was 34% versus 48% in participants with optimum progesterone levels (Melo *et al.*, 2021). To detect a 14% difference in the primary outcome of live birth with >99% power, we originally planned to recruit 900 participants. The study commenced shortly before the COVID-19 pandemic, however, and recruitment was thus substantially hindered by the impact of repeated clinic closures and the de-prioritisation of fertility services. We therefore opted to revise our sample size to a minimum of 396 women, allowing for a power of >70% and an alpha of 5%, and assuming a conservative 1:3 ratio of inadequate versus optimal progesterone levels based on existing literature (Yovich *et al.*, 2015; Labarta *et al.*, 2017, 2021a). We anticipated no loss to follow-up due to the mandatory requirement of reporting assisted reproductive treatment outcomes to the Human Fertilisation and Embryology Authority in the UK.

Statistical analysis

All data analyses were performed using Stata Statistical Software (Release 17, TX, USA). We conducted unadjusted analyses for categorical variables using percentages and the chi-square test, and for continuous variables, we used the Student's *t* test. When comparing the same continuous variable (e.g. serum progesterone) across multiple groups (e.g. different progesterone administration routes), we used a one-way ANOVA test to identify any differences in the means between the various groups.

We conducted unadjusted analyses to investigate the association between serum progesterone deciles and FET outcomes among all participants. We also carried out multilevel mixed-effects multivariable logistic regression analyses to evaluate the association between serum progesterone levels and the treatment outcomes by adjusting for important confounders including participating centre, female age, BMI,

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parity, history of miscarriage, oocyte source (autologous versus donor), FET cycle type (NC FET and HRT FET), exogenous progesterone route, the use of PGT, the number of embryos transferred and embryo quality (top versus non top quality). In this primary model, serum progesterone level was incorporated as a quadratic term to investigate a possible non linear correlation with treatment outcomes. To further evaluate the effect of route of progesterone administration upon the association between serum progesterone and the probability of live birth, we conducted an adjusted subgroup analysis according to luteal phase support regimen (i.e. natural cycle with endogenous progesterone only and programmed cycle with vaginal progesterone only, subcutaneous progesterone only, or combined vaginal plus subcutaneous routes). In a second multivariable logistic regression model, serum progesterone was evaluated as a categorical variable, according to different deciles.

No imputation was required because there were no missing data for any of the confounders of interest. We expressed adjusted estimates as odds ratios (aOR) with 95% CI and judged results to incorporate high statistical confidence where the *P* value was lower than 0.05.

Results

Study population and cycle characteristics

Between 2 January 2020 and 28 February 2021, of a total of 485 eligible women, 402 (82.9%) agreed to participate and were included in the study (Fig. 1). Table I contains details of the participants' baseline and cycle characteristics, including a comparison between women with serum progesterone <10th centile (7.83 ng/ml) and all other participants. The mean participant age (± SD) was 35.3 ± 5.2 years, and the mean BMI ± SD was 25.2 ± 3.7 kg/m^2. Most women underwent HRT FET without pituitary downregulation (237/402, 59.0%) and received exogenous progesterone supplementation through the vaginal route (256/402, 63.7%). The blood samples of three women were deemed unsuitable for analysis by the laboratory, and we were thus unable to include them in the final outcome analysis. One further participant did not undergo embryo transfer due to a failed thaw. A total of 398 women were therefore included in the outcome analysis (Fig. 1). The mean level of serum progesterone on the day of FET was 14.9 ± 7.5 ng/ml. Women with serum progesterone <10th centile

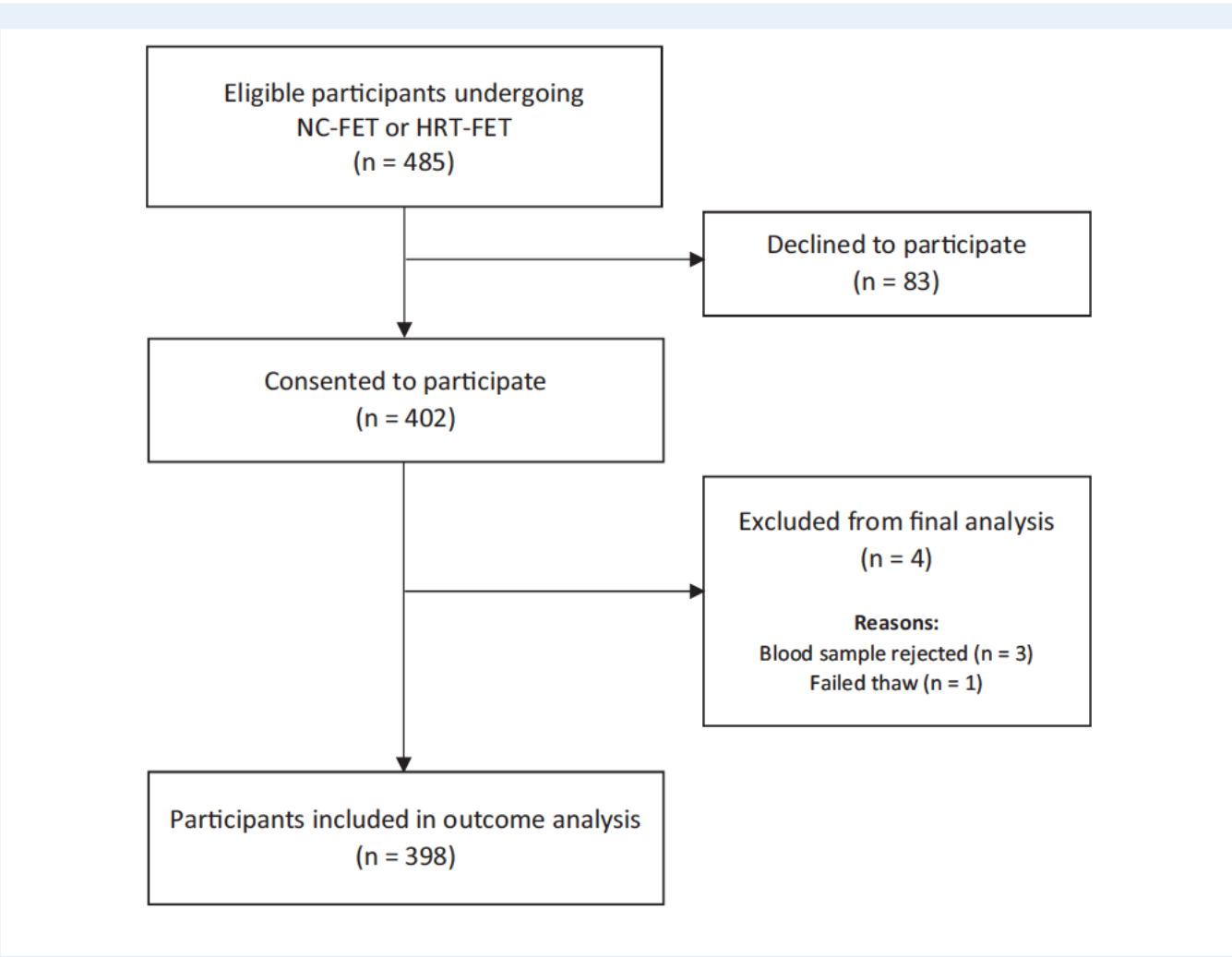


Figure 1. Study flowchart. FET, frozen embryo transfer; NC FET, natural cycle frozen embryo transfer.

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Table I Participant demographics and cycle characteristics.

Characteristic	Total cohort (n = 402)	Serum progesterone <10th centile (<7.83 ng/ml) (n = 39)	Serum progesterone ≥10th centile (≥7.83 ng/ml) (n = 363)	*P* value*
Age (years), mean ± SD	35.3 ± 5.2	33.7 ± 4.4	35.5 ± 5.2	0.053
BMI (kg/m^2), mean ± SD	25.2 ± 3.7	25.4 ± 3.9	25.2 ± 3.7	0.750
Ethnicity				0.095
White	354 (88.1)	29 (74.4)	325 (89.5)	
South Asian	13 (3.2)	2 (5.1)	11 (3.0)	
Black	6 (1.5)	1 (2.6)	5 (1.5)	
Other	28 (7.0)	7 (17.9)	22 (6.0)	
Cause of infertility				0.085
Unexplained	117 (29.1)	7 (18.0)	110 (30.0)	
Male factor	86 (21.4)	8 (20.5)	78 (21.6)	
Female age/ovarian insufficiency	50 (12.4)	7 (18.0)	43 (11.9)	
Anovulation/PCOS	46 (11.4)	6 (15.4)	40 (11.1)	
Tubal pathology	28 (7.0)	5 (12.8)	23 (6.3)	
Other	75 (18.7)	6 (15.3)	69 (19.1)	
Nulliparity	282 (70.1)	21 (53.9)	261 (71.9)	0.025
Previous miscarriage	140 (34.8)	15 (38.5)	125 (34.4)	0.720
Current smoker	7 (1.7)	0	7 (1.9)	1.000
Fresh cycle				
IVF	201 (50.0)	15 (38.5)	186 (51.2)	<0.01
ICSI	195 (48.5)	21 (53.9)	174 (47.9)	
Historic cycle (unknown fertilisation method)	6 (1.5)	3 (7.6)	3 (0.9)	
Donor oocyte use	37 (9.2)	3 (7.7)	34 (9.4)	1.000
PGT-A use	30 (7.5)	1 (2.6)	29 (8.0)	0.340
Time lapse technology use	160 (39.8)	18 (46.2)	142 (39.1)	0.390
Type of FET cycle				0.590
NC FET without exogenous progesterone	35 (8.7)	2 (5.1)	33 (9.1)	
NC FET with exogenous progesterone†	10 (2.5)	0	10 (2.7)	
HRT FET (no downregulation)	237 (59.0)	25 (64.1)	212 (58.4)	
HRT FET (downregulation)	120 (29.8)	12 (30.8)	108 (29.8)	
Progesterone route				0.250
Vaginal only	256 (63.7)	32 (82.1)	224 (61.7)	
Injectable only	57 (14.2)	2 (5.1)	55 (15.1)	
Vaginal plus injectable	54 (13.4)	3 (7.7)	51 (14.1)	
No progesterone	35 (8.7)	2 (5.1)	33 (9.1)	
Number of embryos transferred				1.000
SET	363 (90.5)	36 (92.3)	327 (90.3)	
DET	38 (9.5)	3 (7.7)	35 (9.7)	
Use of at least one top-quality embryo	354 (88.3)	32 (82.1)	322 (89.0)	0.200
Endometrial thickness before FET, mean ± SD	9.6 ± 2.1	9.3 ± 1.6	9.6 ± 2.1	0.380
Serum progesterone (ng/ml), mean ± SD	14.9 ± 7.5	6.0 ± 1.7	15.8 ± 7.2	<0.001

All data are presented as frequency (%) unless stated otherwise.
*For comparison between serum progesterone <10th versus ≥10th centile.
†Vaginal progesterone capsules (n = 9) or pessaries (n = 1) at a dose of 400 mg twice daily.
DET, double embryo transfer; FET, frozen embryo transfer; NC-FET, natural cycle FET; PCOS, polycystic ovary syndrome; PGT-A, preimplantation genetic testing for aneuploidy; SET, single embryo transfer.

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exhibited lower rates of nulliparity (53.9% versus 71.9%, $P=0.025$) and conventional IVF treatment (38.5% versus 51.2%, $P<0.01$) than participants whose serum progesterone was ≥10th centile.

Unadjusted analysis: all cycles

Overall, the live birth rate was 39.2% (156/398), the clinical pregnancy rate was 43.7% (174/398), the implantation rate was 39.9% (174/436), the biochemical pregnancy rate was 55.5% (221/398) and the miscarriage rate was 29.9% (66/221). Figure 2 shows the unadjusted analyses of FET outcomes by serum progesterone decile. The live birth, clinical pregnancy and implantation rates were highest in women whose serum progesterone ranged between the 40th and 50th centiles (>11.98 13.4 ng/ml; live birth rate 48.8% [20/41], clinical pregnancy rate 58.5% [24/41] and implantation rate 53.3% [24/45]). The miscarriage rate was lowest in participants with serum progesterone levels ranging between the 30th and 40th centiles (>10.6 11.98 ng/ml; miscarriage rate 11.8% [2/17]). There were no ectopic pregnancies identified in the study population.

Adjusted analysis: all cycles

When serum progesterone was analysed as a continuous covariate in the multivariable logistic regression model including all routes of progesterone administration, the mean probability of live birth increased non linearly from 37.6% (95% CI 26.3 48.9%) to 45.5% (95% CI 32.1 58.8%) as serum progesterone rose between the 10th and 90th centiles (Fig. 3). Within the same range of serum progesterone levels, the mean probability of miscarriage decreased non linearly from 33.0% (95% CI 20.0 46.0%) to 24.0% (95% CI 10.9 37.1%). The wide CIs precluded the identification of an optimum range of progesterone levels associated with treatment success. However, serum progesterone levels lower than 7.83 ng/ml (10th centile) were confidently associated with a 59% reduction in live birth rate (aOR 0.41, 95% CI 0.18 0.91, $P=0.028$), a 64% lower chance of clinical pregnancy (aOR 0.36, 95% CI 0.16 0.79, $P=0.011$) and a tendency towards higher odds of miscarriage (aOR 2.58, 95% CI 0.88 7.62, $P=0.086$) (Fig. 4).

Unadjusted analysis according to progesterone regimen

The mean serum progesterone level was highest in women using the injectable route (21.10 ± 8.64 ng/ml) and lowest in those receiving vaginal progesterone supplementation in HRT FET cycles (12.69 ± 5.84 ng/ml) ($P<0.001$) (Table II). We did not identify a difference in clinical outcomes for the comparisons of NC FET with exogenous progesterone versus no progesterone, injectable versus no progesterone, and combined routes (vaginal and injectable) versus no progesterone. However, in comparison to NC FET without exogenous progesterone, HRT FET cycles using vaginal progesterone supplementation were associated with higher implantation rates (OR 2.29, 95% CI 1.01 5.54, $P=0.03$), increased odds of biochemical (OR 2.33, 95% CI 1.06 5.19, $P=0.02$) and clinical pregnancy (OR 2.60, 95% CI 1.15 6.33, $P=0.01$), and a tendency towards increased odds of live birth (OR 2.04, 95% CI 0.90 4.95, $P=0.07$).

Adjusted analysis according to progesterone regimen

The association between serum progesterone levels and the probability of live birth appeared to vary according to the FET cycle regimen

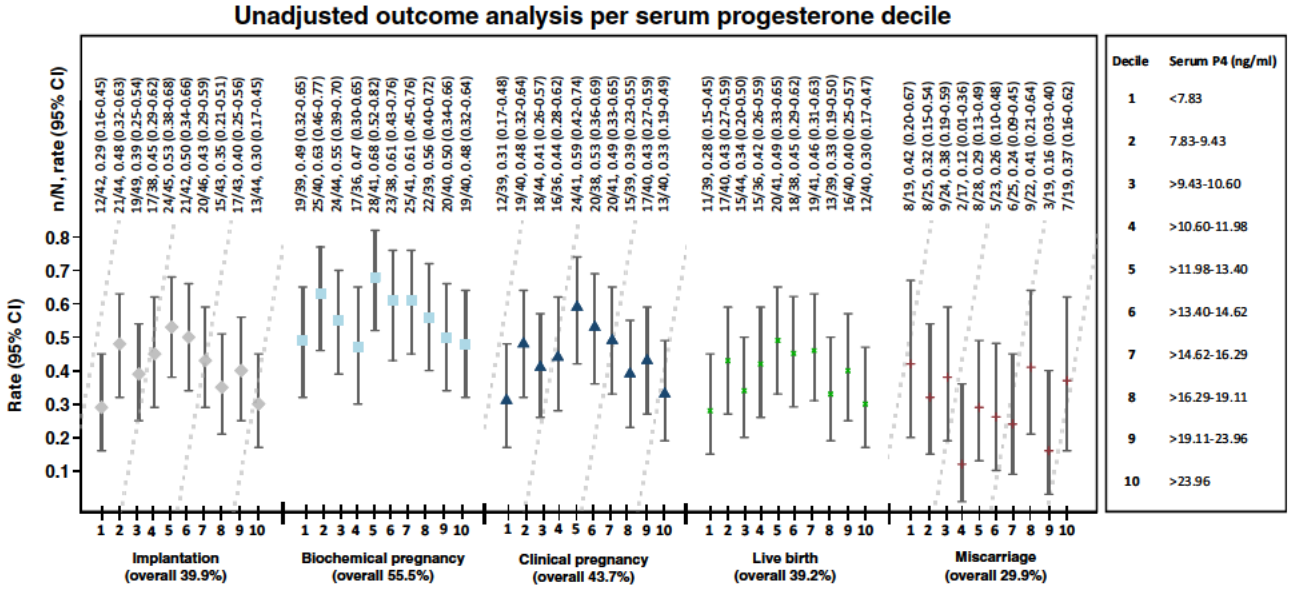


Figure 2. Unadjusted analyses for the primary and secondary outcomes according to serum progesterone deciles. n, number of events; N, total of women analysed within the corresponding serum progesterone decile; P_4, progesterone.

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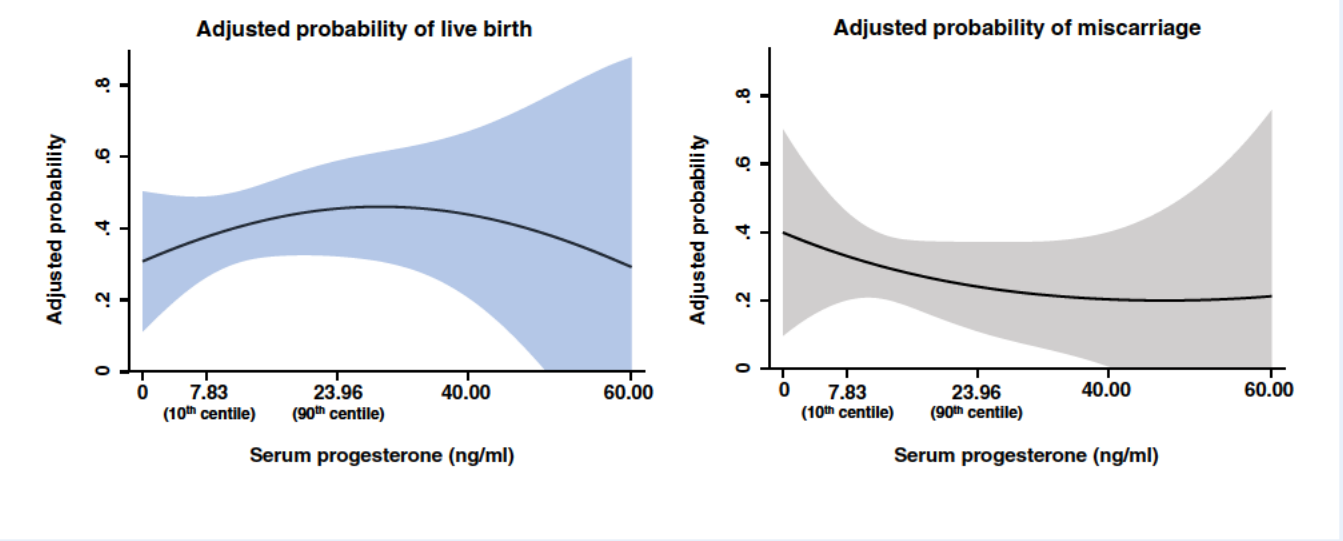


Figure 3. Multivariable regression model describing the adjusted probability of live birth and miscarriage according to serum progesterone levels. The dark line represents the mean adjusted probability, with respective 95% CI in shading. Model adjusted for recruiting centre, age, BMI, oocyte source, use of preimplantation genetic testing, history of miscarriage, parity, type of cycle (natural versus pro grammed), progesterone route of administration, number of embryos transferred and embryo quality (top versus non top).

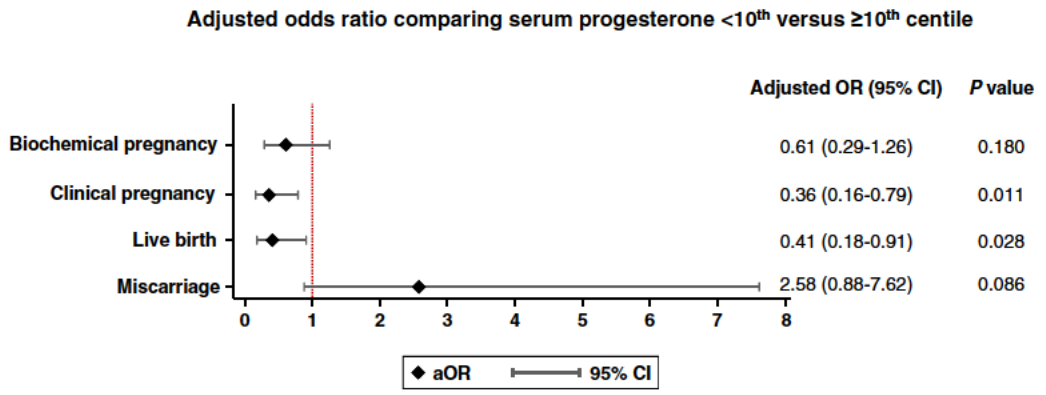


Figure 4. Forest plots describing the adjusted effect of progesterone levels <10th centile (<7.83 ng/ml) on the main clinical outcomes of clinical pregnancy, live birth and miscarriage rates in comparison with serum progesterone ≥10th centile (≥7.83 ng/ml, reference). Multivariable logistic regression model adjusted for recruiting centre, age, BMI, oocyte source, use of preim plantation genetic testing, history of miscarriage, parity, type of cycle (natural versus programmed), route of progesterone administration, number of embryos transferred and embryo quality (top versus non top). aOR, adjusted odds ratio.

(Fig. 5). In NC FET cycles relying exclusively on endogenous progester one synthesis, the mean probability of live birth increased to a maxi mum of 53.9% (95% CI 23.7 84.1%) as progesterone levels reached 20.3 ng/ml, and declined slightly beyond this level of serum progester one. In women undergoing HRT cycles with vaginal progesterone, the mean probability of live birth increased approximately linearly as serum progesterone rose. Women having HRT FET with only subcutaneous exogenous progesterone exhibited an increase in the mean adjusted probability of live birth up to a level of 16.3 ng/ml (maximum probabil ity 36.4%, 95% CI 19.2 53.5%), beyond which treatment success appeared to decline steeply. Lastly, the combined use of vaginal and subcutaneous progesterone resulted in little evidence of variation in the mean probability of live birth according to serum progesterone, ranging between 36% and 38.4%. However, CIs were wide for all pro gesterone routes. The low number of women having NC FET with ex ogenous progesterone (n = 10) precluded multivariable logistic

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Table II Treatment outcomes according to progesterone regimen.

	NC-FET no progesterone (n = 35)	Crude OR (95% CI)	NC-FET vaginal P_4 (n = 10)	Crude OR (95% CI)*	HRT-FET vaginal P_4 (n = 245)	Crude OR (95% CI)	HRT-FET subcutaneous P_4 (n = 57)	Crude OR (95% CI)	HRT-FET combined vaginal and subcutaneous P_4 (n = 54)	Crude OR (95% CI)	*P* value for ANOVA
Serum progesterone (ng/ml), mean ± SD	4 75 ± 4 74	–	4 46 ± 3 40	–	2 69 ± 5 84	–	2 0 ± 8 64	–	8 4 ± 9 75	–	<0 00
Implantation rate	0/35 (28 6)	Ref	0/ 0 (0)	0 (0– 05) *P* = 0 06	30/272 (47 8)	2 29 (0 –5 54) *P* = 0 03	7/60 (28 3)	0 99 (0 40–2 45) *P* = 00	23/62 (37)	47 (0 6 –3 56) *P* = 0 50	–
Biochemical pregnancy	4 (40 0)	Ref	2 (20 0)	0 38 (0 04–2 34) *P* = 0 24	49 (60 8)	2 33 (06–5 9) *P* = 0 02	27 (47 4)	35 (0 58–3 7) *P* = 0 52	3 (57 4)	2 02 (0 85–4 80) *P* = 0 3	–
Clinical pregnancy	0 (28 6)	Ref	0 (0)	0 (0– 05) *P* = 0 06	25 (5 0)	2 60 (5–6 33) *P* = 0 0	7 (29 8)	06 (0 42–2 69) *P* = 00	23 (42 6)	86 (0 75–4 6) *P* = 0 26	–
Miscarriage	4 (28 6)	Ref	2 (00)	nestimab e	38 (25 5)	0 86 (0 23–3 96) *P* = 0 80	(40 7)	72 (0 43–6 90) *P* = 0 5	(35 5)	38 (0 35–5 43) *P* = 0 74	–
Live birth	0 (28 6)	Ref	0 (0)	0 (0– 05) *P* = 0 06	0 (43)	2 04 (0 90–4 95) *P* = 0 07	6 (28)	0 98 (0 38–2 48) *P* = 00	20 (37 0)	47 (0 59–3 68) *P* = 0 49	–

All data are presented as frequency (%) unless otherwise stated.
*Odds ratios were calculated with the Cornfield approximation where event numbers were 0.
FET, frozen embryo transfer; NC, natural cycle; OR, odds radio; P_4, progesterone; Ref, reference group.

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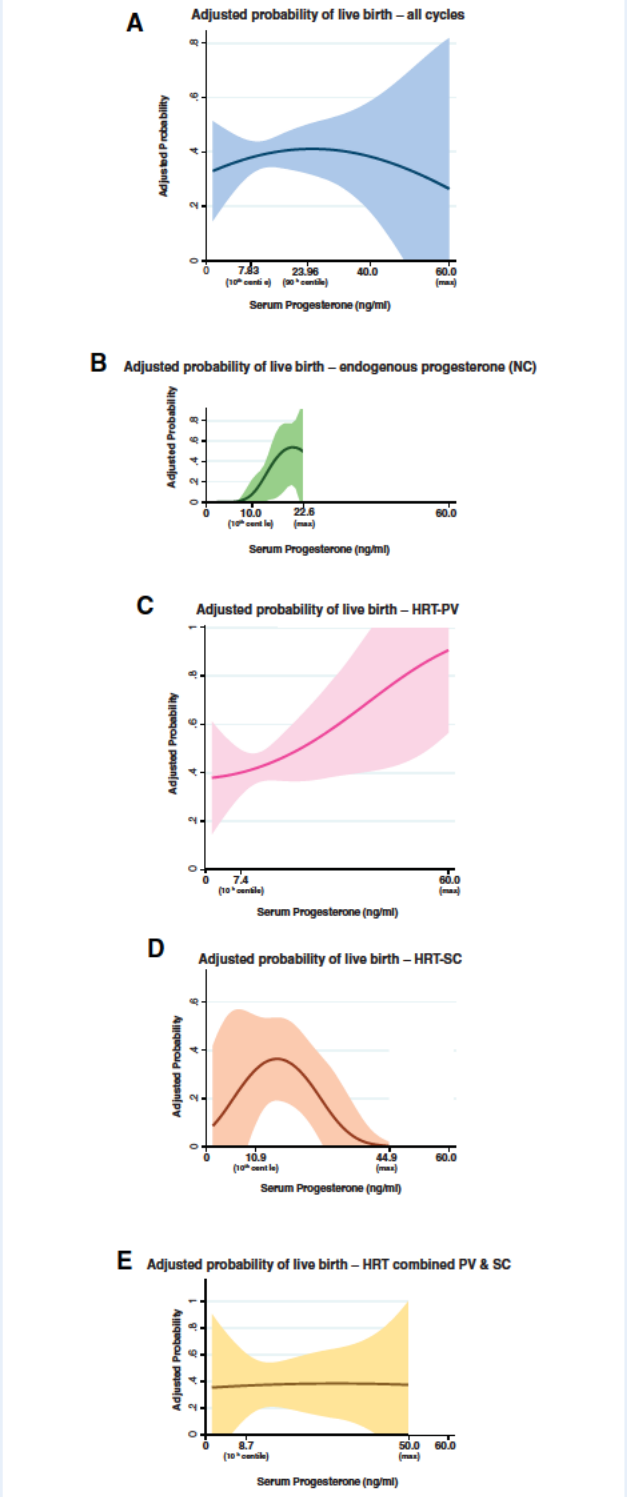


Figure 5. Multivariable regression model describing the association between serum progesterone levels and the adjusted probability of live birth according to route of progesterone administration. (**A**) All cycles, irrespective of route. (**B**) Natural cycle FET. (**C**) HRT cycle, vaginal route. (**D**) HRT cycle, subcutaneous route. (**E**) HRT cycle, combined vaginal and subcutaneous routes. The dark line represents the mean adjusted probability, with respective 95% CI in shading. (A) Model adjusted for recruiting centre, age, BMI, oocyte source, use of preimplantation genetic testing, history of miscarriage, parity, type of cycle (natural versus programmed), progesterone route of administration and number of embryos transferred and embryo quality (top versus non top). (B E) Model adjusted for recruiting centre, age, BMI, oocyte source, use of preimplantation genetic testing, history of miscarriage, parity, number of embryos transferred and embryo quality (top versus non top). FET, frozen embryo transfer; NC, natural cycle; PV, vaginal route; SC, subcutaneous route.

regression investigating the association between serum progesterone levels and the probability of live birth in this subgroup.

Discussion

Summary of evidence

In this prospective multicentre cohort study, we investigated the association between serum luteal progesterone and treatment outcomes in women undergoing FET across eight fertility clinics in the UK. Our results support the hypothesis that low serum progesterone is associated with reduced treatment success in FET. Below the 10th centile (~7.8 ng/ml), the rates of clinical pregnancy and live birth were reduced, and the risk of miscarriage tended to increase. In women having a natural cycle without exogenous progesterone or HRT FET treatment using vaginal progesterone, our adjusted analyses suggested a positive correlation between serum progesterone levels and the mean probability of live birth. However, this association appeared to be non linear for women receiving subcutaneous progesterone only, in whom both lower and higher serum progesterone levels were associated with a decrease in the mean probability of live birth. Further, the mean probability of live birth remained stable in women receiving combined vaginal and subcutaneous progesterone, irrespective of serum progesterone levels.

The hypothesis that FET success may be affected by an insufficient luteal phase has only recently been evaluated. In a systematic review of studies investigating the association between serum luteal progesterone and FET outcomes, we found that for cut off levels below 10 ng/ml, women with lower serum progesterone experienced fewer ongoing pregnancies or live births, a reduction in clinical pregnancy rate and increased risk of miscarriage (Melo *et al.*, 2021). These findings were limited to studies where only vaginal progesterone had been used in HRT FET cycles, however, and there was a paucity of prospective evidence on NC FET and HRT FET treatment using non vaginal routes of progesterone administration. In addition, our review identified a need for prospective data investigating serum progesterone in a continuous fashion rather than focusing on the 'high' versus 'low' dichotomy. The present study addresses the existing knowledge gaps by including all women undergoing FET treatment, regardless of cycle type or progesterone administration route, and by approaching serum progesterone as a continuous variable when adjusting for confounders. Our results support the hypothesis that there is a minimum level of serum progesterone required for successful implantation and placentation in FET cycles, in addition to offering further insight into the effect

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modifying role exerted by different routes of progesterone administration.

Although progesterone measurements below the 10th centile were associated with worse outcomes in this cohort, our adjusted percentile analyses did not categorically demonstrate a linear increase in live birth rates as serum progesterone measurements rose beyond this level. The adjusted analyses suggest that serum progesterone levels above the 90th centile may have in fact been associated with a reduction in the mean probability of live birth and a slight increase in the risk of miscarriage, although the wide CIs precluded any conclusive determi nations of effect size. Whether high serum progesterone may be detri mental to pregnancy outcomes has been the subject of some debate, and the evidence in FET cycles remains uncertain (Kofinas *et al.*, 2015; Yovich *et al.*, 2015; Alsbjerg *et al.*, 2020; Melo *et al.*, 2021). In a study by Liang *et al.* (2018), excessive progesterone in pregnant mice was found to be just as deleterious to endometrial receptivity and decidual isation as low progesterone. The authors did not evaluate serum pro gesterone levels, however, and focused instead on the intravenous administration of successively higher progesterone doses.

There has been substantial controversy in the literature on the opti mum route of progesterone administration in FET. In a seminal three arm trial by Devine *et al.* (2021) including 1125 women undergoing FET, the authors randomly allocated participants to endometrial prepa ration using daily intramuscular progesterone (50 mg), daily vaginal micronised progesterone plus intramuscular progesterone every 3 days, or daily vaginal micronised progesterone only. Women in the vaginal only arm had a lower live birth rate than those in the other two groups, driven by an increased incidence of miscarriage identified in an interim analysis (Devine *et al.*, 2018). This resulted in the premature termination of the vaginal only treatment arm. However, the relatively low dose of vaginal progesterone (200 mg twice daily) may have contributed to these results, in which case the use of a systemic route of administration may have led to luteal rescue in the combination therapy arm. Crucially, the incidence of miscarriage per pregnancy was highest (80%), and the live birth rate per participant was lowest (33%) in women with very low serum progesterone (<1 ng/ml) measured 2 weeks after FET, although the investigators did not present analyses adjusted for the route of ad ministration. In our study, women who exclusively received injectable progesterone (25 mg subcutaneously twice daily) had the highest circu lating progesterone levels. Yet in the unadjusted analysis according to progesterone administration route, those who only took injectable pro gesterone also experienced the lowest number of live births and clinical pregnancies. In addition, the adjusted analyses according to route of ad ministration suggest that the mean probability of live birth increased as serum progesterone levels rose to 16 3 ng/ml, beyond which the mean probability of treatment success declined. This appears to be in stark contrast with the findings of the aforementioned randomised controlled trial, and it may be explained in part by the difference in pharmacokinet ics between the intramuscular and subcutaneous routes.

The use of subcutaneous progesterone for luteal phase support has become increasingly common in the past decade, although the vaginal and intramuscular routes remain the most used worldwide (Shoham *et al.*, 2021). While data comparing different dosages of the aqueous subcutaneous (25 mg OD versus 50 mg OD) have not identified differ ences in endometrial decidualisation (de Ziegler *et al.*, 2013), there remains a paucity of studies investigating pregnancy outcomes in women having luteal phase support with aqueous versus oil based formulations. Evidence suggests that the subcutaneous administration of 25 mg progesterone in aqueous solution results in maximum plasma concentrations within 2 hr, rapidly followed by a drop to <10 ng/ml in some women within the first 8 hr of administration, whereas the in tramuscular route in oil solution confidently leads to sustained serum levels >20 30 ng/ml for at least 24 hr (Sator *et al.*, 2013). In our co hort, it is possible that by performing venepuncture 4 6 hr after the last subcutaneous injection, we may have obtained high serum proges terone measurements that failed to reflect potentially subtherapeutic levels shortly thereafter, extending to low trough concentrations right before the next progesterone dose. However, this does not ade quately explain why live birth rates decreased substantially beyond se rum progesterone levels of 16.3 ng/ml in this subgroup of women. It is possible that such a phenomenon may have stemmed from decreased responsiveness of uterine receptors to increasing systemic progester one levels, especially in the absence of a compensatory effect other wise exerted by vaginal progesterone and its 'first uterine pass' effect (Chrousos *et al.*, 1986). In addition, recent data suggest that there may not be an association between serum progesterone levels, uterine progesterone levels and endometrial receptivity as measured by tran scriptomic analysis (Labarta *et al.*, 2021b).

In women undergoing HRT FET with vaginal progesterone, recent studies have suggested that additional supplementation using a second route of administration may lead to luteal rescue where serum pro gesterone levels are low (Álvarez *et al.*, 2021; Yarali *et al.*, 2021; Labarta *et al.*, 2021a). Álvarez *et al.* (2021) conducted a prospective non randomised interventional study where 453 women having pro grammed FET with vaginal progesterone underwent venepuncture and serum measurement of progesterone levels on the day before euploid embryo transfer. Those whose serum progesterone was <10.6 ng/ml received additional subcutaneous progesterone from the day of FET and experienced similar rates of clinical pregnancy, live birth and mis carriage to those of participants with progesterone levels ≥10.6 ng/ml. In a subsequent study, Labarta *et al.* (2022) retrospectively analysed 2275 women having HRT FET with micronised vaginal progesterone. The authors added subcutaneous progesterone for luteal phase sup port in women whose serum progesterone was <9.2 ng/ml on the day of FET, and demonstrated non inferior clinical outcomes in com parison to the group where serum progesterone was ≥9.2 ng/ml. In both studies, the intervention was based upon a single venepuncture and serum progesterone measurement, suggesting that once an addi tional route of progesterone administration has been commenced, there may be little value in obtaining serial progesterone levels. The results of our study are in line with these findings by demonstrating that in women who received combined vaginal and subcutaneous progesterone, the probability of live birth exhibited little variation in relation to serum progesterone levels. Although some may argue that these results support the universal use of combined vaginal and subcu taneous progesterone in HRT FET, it must be noted that such an ap proach might also result in added adverse events and treatment costs.

The mechanisms through which different routes of exogenous pro gesterone may act synergistically have not been fully clarified. In natu ral conception, the corpus luteum secretes progesterone into microvessels that feed into the pelvic vasculature and, in turn, the sys temic circulation (Takasaki *et al.*, 2009; Han *et al.*, 2019). It is thus plausible to consider that low serum progesterone levels may consti tute a proxy marker of a hypoprogestogenic state and insufficient

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luteal support (Verhaegen et al., 2012). In the uterus, progesterone has been shown to facilitate decidualisation and embryo implantation by inducing an optimum immune endocrine milieu within the endometrial lining (Shah et al., 2019; Pereira et al., 2021). Progesterone also acts upon the myometrium, reducing its contractility and therefore leading to a state of mechanical quiescence which is additionally thought to aid early placentation (Mueller et al., 2006; Moliner et al., 2021; Pereira et al., 2021). Systemically, progesterone exerts a regulatory role upon the innate and acquired immune responses, resulting in an inhibition of cytotoxicity and the induction of immune tolerance required for successful implantation (Szekeres Bartho, 2018; Shah et al., 2019). The bioavailability of progesterone administered vaginally varies according to many factors including dose, frequency of administration, the woman's age and BMI, the saturability of vaginal and uterine progesterone receptors, and the ability of the epithelial lining to absorb the drug into the systemic circulation (MacLaughlin and Richardson, 1976; Levy et al., 1980; Archer et al., 1995; González Foruria et al., 2020; Whynott et al., 2021). There is, hence, biological plausibility to the hypothesis that in women with a low level of circulating progesterone, the addition of a systemic route of exogenous progesterone administration may compensate, at least partly, for low absorption rates where there is impaired local absorption. By the same token, it is also reasonable to postulate that injectable progesterone in isolation, while capable of achieving high serum progesterone levels, may not guarantee sufficient uterine supply, possibly exerting a deleterious effect on treatment success.

Recent evidence suggests that HRT FET cycles are associated with a substantial increase in the risk of hypertensive disorders of pregnancy compared to NC FET, possibly owing to the lack of a corpus luteum (von Versen Höynck et al., 2019; Wang et al., 2020). It is thought that luteal secretory products other than progesterone, including relaxin 2, may exert a modulatory effect upon the uterine vasculature and thus facilitate normal implantation (Pereira et al., 2021). These data have led some researchers to support a move towards favouring the use of NC FET for improved safety and non inferior effectiveness compared to HRT FET (von Versen Höynck and Griesinger, 2022). While studies investigating the association between serum progesterone and NC FET outcomes remain scarce, observational data show that low serum progesterone may be nefarious to live birth rates in NC FET (Gaggiotti Marre et al., 2020). These findings add strength to the concept of luteal phase defect in NC FET and are further corroborated by evidence suggesting that LPS in NC FET results in improved treatment outcomes (Mizrachi et al., 2021).

Strengths and limitations

The prospective nature of this study, its multicentre design and the blinding of participants and personnel are its major strengths. We collected extensive demographic and endpoint data for all participants, allowing for robust adjusted analyses that confidently identified an independent effect of serum progesterone upon FET outcomes accounting for possible confounders such as the inclusion of different FET regimens. Our findings corroborate those of other studies where only vaginal progesterone was administered (Labarta et al., 2017, 2022), in addition to offering further insight into the association between serum progesterone and live birth in NC FET and HRT FET cycles using non vaginal routes of progesterone administration.

The principal limitation of our study is that instead of the originally planned 900 participants, we could only recruit 402 women due to constraints linked to the COVID 19 pandemic. We based our revised calculation upon a systematic review of the literature, however, and were able to reach satisfactory power (>70%) to detect a meaningful difference between optimal and inadequate serum progesterone levels. In addition, our cohort did not include women receiving oral (e.g. dydrogesterone) and rectal progestogens, and therefore our findings may not be generalisable to these two routes of administration. Although dydrogesterone has been increasingly administered in recent years for luteal phase support, this remains uncommon in the UK. Importantly, Vuong et al. (2021) prospectively compared the use of micronised vaginal progesterone alone versus in combination with oral dydrogesterone and found higher live birth rates in women receiving combined therapy. This requires further corroboration, because the oral route may offer improved convenience to women undergoing treatment. Nonetheless, allocation to the two treatment arms was not based upon serum progesterone measurements, and there was in fact no difference in serum progesterone levels between the two groups (Vuong et al., 2021). The use of rectal progesterone has been shown to result in similar serum levels to the vaginal route (Nillius and Johansson, 1971). Although there is evidence on the effect of the combined rectal plus vaginal routes of progesterone upon FET outcomes (Alsbjerg et al., 2020), the former has not been studied in isolation.

An additional limitation of our study relates to its pragmatic nature. We pre specified to include all women undergoing FET, regardless of treatment protocol. Prospectively collected data allowed for robust multivariable logistic regression analyses, yet it is possible that some residual confounding may have remained. For example, the choice of FET regimen was left to the discretion of the attending physician and participants, which might have been influenced by participants' characteristics (e.g. BMI or history of pregnancy loss). However, our adjusted analyses considered such confounders, thus minimising the risk of bias. Furthermore, among women receiving exclusively vaginal progesterone (n = 256), a minority (n = 12) had the 400 mg TDS regimen and 244 women received the 400 mg BD regimen. We conducted a post hoc sensitivity analysis for women receiving vaginal progesterone adjusting for dose, and this did not change the primary findings.

Lastly, the timing of serum progesterone measurement varied between different participating centres, and it was not possible to account for this due to the pragmatic nature of our study. In women who received exogenous progesterone, this may have not affected the reliability of serum progesterone results, because most progesterone formulations lead to a steady state concentration of progesterone within 24 72 hr (Levy et al., 2000; Corleta et al., 2004; Paulson et al., 2014; Cometti, 2015). In participants undergoing NC FET, the accuracy of serum progesterone measurements may have been affected by the pulsatile fashion in which the corpus luteum secretes progesterone (Filicori et al., 1984), although the study by Gaggiotti Marre et al. (2020) suggested a good correlation between serum progesterone and treatment outcomes in NC FET.

Conclusions

Our results corroborate existing evidence suggesting that low serum progesterone levels hinder FET success. However, the relationship

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between serum progesterone and the probability of live birth appears to be non linear in women receiving exclusively subcutaneous progesterone, suggesting that in this subgroup of women, high serum progesterone may also be detrimental to treatment success.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Authors' roles

P.M., A.T. and A.C. conceived and designed the study. P.M. collated the data, performed the analyses and wrote the article. C.E. and M.J.P. provided statistical input. S.W., G.P., Y.C., C.E., M.J.P., S.F., M.K., C.K., P.L., M.R., V.S., S.P., R.K., D.W., J.G., M.W., I.G., A.T. and A.C. provided critical input into the final article. All authors approved the final version and accept responsibility for the article as published.

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Conflict of interest

S.F. is a minor shareholder of CARE Fertility but has no financial or other interest with progesterone testing or manufacturing companies. P.L. reports personal fees from Pharmasure, outside the submitted work. G.P. reports personal fees from Besins Healthcare, outside the submitted work. M.W. reports personal fees from Ferring Pharmaceuticals, outside the submitted work. The remaining authors have no conflict of interest to declare. The remaining authors have no conflict of interest to declare.

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CHAPTER 5: EVIDENCE FOR THE EFFECTIVENESS OF IMMUNOLOGICAL THERAPIES IN WOMEN WITH SUBFERTILITY AND/OR UNDERGOING ASSISTED REPRODUCTION

Preamble

Chapters 3 and 4 focused on the essential role of progesterone during the luteal phase, including its immunomodulating effects. Chapter 5 delves further into the importance of immune regulation in the luteal phase by synthesising the evidence on immunological therapies in women with subfertility and/or assisted conception.

This chapter was published in *Fertility and Sterility* in 2022. Appendix 10 contains details of protocol registration on PROSPERO, and appendix 11 presents a full description of the methods.

Authors' contributions

Dr Pedro Melo registered the protocol, designed and performed the searches, led the study selection, data extraction, quality assessment and analyses, and drafted the initial review manuscript. Dr Thornton acted as second reviewer by independently participating in the study selection, data extraction and quality assessment. Professor Coomarasamy provided important critical input into the review process and manuscript. Professor Granne provided important critical input into the review design and protocol, and edited the original manuscript extensively.

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Evidence for the effectiveness of immunologic therapies in women with subfertility and/or undergoing assisted reproduction

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Implantation is a critical step in the establishment of a successful pregnancy, depending on a complex immune endocrine dialogue between the developing embryo and maternal endometrium. Research suggests that altered immunity in the maternal decidua results in implantation impairment and failure. Immunomodulatory drugs have, thus, been widely used in assisted conception to aid embryo implantation, despite an absence of consensus on their effectiveness and safety. We conducted a systematic review and meta analysis of interventional studies investigating the use of immunomodulators in women undergoing assisted reproduction. Evidence was uncertain of an effect for most of the included interventions, owing to heterogeneous findings and a paucity of high quality studies. For certain patient subgroups, however, the use of specific immunomodulatory therapies may offer some benefit. There is a need for further large randomized controlled trials to corroborate these findings. (Fertil Steril® 2022;117:1144 59. ©2022 by American Society for Reproductive Medicine.)

Key Words: Immunomodulatory drugs, implantation, infertility

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The number of patients undergoing assisted reproductive technology (ART) for fertility treatment continues to increase. Yet, despite advances over the past decades, most ART cycles do not result in a live birth. Even when chromosomally normal embryos are transferred, only approximately 50% will implant (1). Implantation failure remains the likely outcome of most in vitro fertilization (IVF) cycles, and approximately 10% of women undergoing IVF are thought to experience recurrent implantation failure (RIF), although there remains no universally agreed definition (2).

Critical to successful implantation is the adequate decidualization of the endometrium. Endometrial immune cells are key to the transformation of the decidua into a receptive mucosa that will permit embryo attachment and implantation. This highly regulated response involving an influx of innate immune cells, including macrophages, dendritic cells, and neutrophils, in addition to a large population of natural killer (NK) cells, results in an inflammatory environment at the time of conception and implantation (3). However, this response is dynamic; recent data indicate that by the early first trimester, maternal immune inflammatory responses are restrained and modulated by complex and diverse signaling between fetal trophoblast cells and decidual immune cells (4).

Given the complexity of the implantation process, several factors may contribute to the failure of an embryo to implant, not least embryo aneuploidy. However, there has been much focus both in the scientific community and from patients on how the maternal immune response influences implantation and whether modulating maternal immunity can improve the ART success rates. For some patients and clinicians, the concept of embryo rejection has been an attractive one, on the basis of the knowledge that a specialized type of NK cell is the predominant immune cell in the peri-implantation endometrium. This concept of embryo rejection has often been given unscientific credibility simply because of its name.

Immunomodulators may be offered empirically to patients with a history of

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implantation failure where a clinician believes that there may be an immune mechanism underlying this or because specific immune cell testing has been undertaken and found to be abnormal. Blood NK cell testing (with or without associated cytotoxicity assays) is commonly offered, despite the fact that circulating NK cells are phenotypically and functionally different from their specialized endometrial counterparts (5) and their numbers are not correlated with endometrial NK cells (6). Neither blood nor endometrial NK cells have been robustly demonstrated to be associated with subfertility or RIF (7). After some studies reported alterations in the expression of T helper (Th)1 and Th2 cytokines in circulating T cells, tests including measurement of Th1/Th2 cytokine ratios have also found their way into clinical practice (8–10). Others have reported an association between RIF and altered ratios of cytokine messenger ribonucleic acid within the endometrium, including interleukin (IL-)15, IL-18, and tumor necrosis factor (TNF)-like weak inducer of apoptosis, hypothesizing that immunomodulators may improve the implantation rates in such patients (11). Additionally, some clinics test for autoantibodies, such as antinuclear, antiphospholipid, and thyroid autoantibodies. Although there may be associations with autoantibodies and infertility, causal links remain to be established (12).

Immunologic treatments have been used for decades in ART. Recent data have shown that up to 1 in 4 women undergoing IVF treatment may use add-on therapies, such as aspirin, heparin, or corticosteroids (13–16). Although less commonly used, other drugs, such as intralipid, intravenous immunoglobulin (IVIG), granulocyte colony-stimulating factor (G-CSF) and TNF alpha (TNF-α) inhibitors, are also administered to ART patients (15).

We have systematically reviewed the literature to evaluate the effectiveness and safety of immunomodulatory therapies used commonly in clinical practice and consider their potential mechanisms of action in the context of subfertility, ART, and implantation failure. We included randomized and nonrandomized interventional full-text studies where outcome data were reported per participant. Trials investigating participants with recurrent pregnancy loss were excluded. The primary effectiveness outcome considered in this review was the composite rate of ongoing pregnancy rate (OPR) or live birth rate (LBR) per participant. Ongoing pregnancy was defined as a viable intrauterine pregnancy at $\geq$12 weeks of gestation identified on ultrasound, and live birth was defined as the delivery of a live fetus after 22 weeks of pregnancy (17). Where possible, we performed meta-analysis of randomized controlled trials (RCTs) using a random-effects model and considered heterogeneity to be substantial where $I^2 > 50\%$. Subgroup analyses were also undertaken where data were available for women with previous implantation failure, known autoimmunity, and conditions hypothesized to be associated with an altered inflammatory response (e.g., elevated NK cell activity or numbers).

ASPIRIN

Low-dose aspirin is one of the most widely used adjuvants in ART (15). Aspirin inhibits cyclooxygenase (COX) in platelets, preventing the conversion of arachidonic acid into prostaglandins and, thus, inhibiting thromboxane production (18). There are 2 types of COX: 1 and 2. By irreversibly inhibiting both COXs 1 and 2, aspirin may improve uterine and ovarian blood flow and reduce inflammation, all of which may enhance fertility or the success of ART (19, 20).

There have been numerous studies investigating aspirin for women with subfertility undergoing ART (21–23). We identified 12 studies that reported the OPR or LBR comparing the use of aspirin vs. a placebo or no intervention (21, 24–34) (Table 1). Most of the 6 nonrandomized studies reported uncertain findings (21, 24–27) except for that of Frattarelli et al. (28), where the use of aspirin was associated with a 20% increase in the LBR compared with that of placebo (relative risk [RR], 1.20; 95% confidence interval [CI], 1.04–1.38). The 6 RCTs that reported the OPR or LBR included 1,319 participants (29–34). Meta-analysis of these RCTs showed that aspirin probably makes little or no difference to the OPR or LBR (RR, 1.04; 95% CI, 0.81–1.33; 6 RCTs; $I^2 = 28\%$; moderate-certainty evidence) (Fig. 1 and Table 2). None of these studies reported significant adverse events although aspirin is known to be associated with gastrointestinal disturbances and bleeding. Albeit very commonly used by women undergoing ART, we did not find evidence that aspirin improved pregnancy outcomes. In addition, the subgroup analyses of good-prognosis patients, women with at least 1 previous implantation failure or a thin endometrium did not alter these findings, and therefore, recommending aspirin to patients undergoing ART to date has no evidence-based justification.

HEPARIN

In addition to its antithrombotic effects, there are several mechanisms by which heparin has been hypothesized to influence implantation. Both unfractionated heparin and low-molecular-weight heparin (LMWH) modulate insulin-like growth factors 1 and 2, which in turn may facilitate trophoblast invasion. Heparin may also increase the decidual expression and secretion of heparin-binding epidermal growth factor, which has been shown to promote an invasive trophoblast phenotype (35). In addition, heparin may promote trophoblast invasion by inducing matrix metalloproteinase activity with a concomitant suppression of tissue inhibitors of matrix metalloproteinases (36, 37).

Three cohort studies reported uncertain findings as to the effect of heparin on the LBR (21, 38, 39). Additionally, we identified 3 RCTs including 386 women that reported the LBR (40–42). Our meta-analysis did not demonstrate an increase in the LBR in patients receiving subcutaneous LMWH, although the quality of the evidence was assessed as being of very low certainty (RR, 1.55; 95% CI, 0.80–3.00; 3 RCTs; $I^2 = 51\%$) (Fig. 1 and Table 2).

Heparin is a drug with a good safety profile in pregnancy. Nevertheless, the evidence to date does not support its use routinely in women with subfertility. Importantly, heparin may cause bruising and discomfort around the injection site as well as bleeding, although in the studies included in this analysis, adverse events were reported in

TABLE 1

Characteristics of included studies reporting on the ongoing pregnancy or live birth rate.

Interventions	Study	Country	Design	Duration	Population	Inclusion criteria	Subgroup	Total analyzed	Outcome
Aspirin	Chen et al. (2017) (24)	People's Republic of China	Prospective cohort	January 2015 to December 2015	IVF	Age of <40 y; serum autoantibodies; normal karyotype; no infectious diseases; normal basal level of hormones; normal uterine anatomy	Autoimmunity	76	LBR
	Dirckx et al. (2009) (29)	Belgium	RCT	Unstated	IVF	First IVF/ICSI cycle	Unselected	201	LBR
	Frattarelli et al. (2006) (28)	USA	Retrospective cohort	January 2000 to August 2003	IVF	Egg recipient cycles	Low ovarian response	460	LBR
	Frattarelli et al. (2008) (25)	USA	Retrospective cohort	January 2000 to July 2006	IVF	Low responding women	Low ovarian response	1,250	LBR
	Gizzo et al. (2014) (26)	Italy	Prospective cohort	January 2010 to December 2012	IVF	Age of 25 45 y; normal ovarian response; previous 1 2 failed IVF/ICSI cycles	Previous IF (≥1)	206	OPR
	Haapsamo et al. (2010) (30)	Finland	RCT	Unstated	IVF	Age of <40 y; <4 ovarian stimulations; no contraindications for aspirin	Good prognosis	487	LBR
	Hurst et al. (2005) (27)	USA	Retrospective cohort	1995 to 2001	IVF	Unstated consecutive cycles	Unselected	316	LBR
	Lambers et al. (2009) (31)	The Netherlands	RCT	Unstated	IVF	Age of <39 y; FSH level of ≤10 IU/L; ≥1 previous failed IVF/ICSI treatment	Previous IF (≥1)	169	OPR
	Madani et al. (2019) (32)	Iran	RCT	May 2012 to February 2015	IVF	Age of <40 y; FET; no history of uterine surgery; no uterine disorders, endometriosis, RPL or contraindications to aspirin	Good prognosis	60	LBR
	Pakkila et al. (2005) (33)	Finland	RCT	2000 to 2003	IVF	Age of <40 y; <4 previous ovarian stimulation cycles; no contraindication for aspirin	Good prognosis	374	LBR
	Weckstein et al. (1997) (34)	USA	RCT	September 1993 to January 1995	IVF	Oocyte recipient cycles; thin endometrium (<8 mm); normal uterine cavity	Thin endometrium	28	LBR
LMWH (subcutaneous)	Berker et al. (2011) (38)	Turkey	Prospective cohort	June 2007 to October 2009	IVF	2 previous IFs; normal uterine; normal hormone profile; negative thrombophilia screening	Previous IF (≥1)	207	LBR
	Noci et al. (2011) (40)	Italy	RCT	May 2008 to December 2008	IVF	Age of <40 y; no congenital or acquired thrombophilia; no recent treatment with LMWH; no endocrine/hematologic abnormalities, chronic diseases, or tubal or uterine pathology interfering with embryo implantation	Good prognosis	153	LBR
	Qublan et al. (2008) (41)	Jordan	RCT	October 2004 to March 2006	IVF	Age of 19 35 y; ≥3 previous IVF failures; basal FSH level of ≤10 IU/L; BMI of 19 29 kg/m^2; presence of both ovaries; ≥3 previous IVF failures; good quality embryos for transfer; endometrial thickness of 8 14 mm; GnRH agonist down regulation protocol	Previous IF (≥1)	83	LBR
	Urman et al. (2009) (42)	Turkey	RCT	January 2006 to May 2008	IVF	≥2 failed previously fresh embryo transfer cycles; age of ≤38 y; fresh ejaculate sperm to be used for ICSI; no hormonal, coagulation, or immunologic disorders; normal uterine cavity as assessed by hysteroscopy or saline infusion sonography; normal female and male peripheral karyotype	Previous IF (≥1)	150	LBR
	Siristatidis et al. (2018) (39)	Greece	Retrospective cohort	February 2012 to June 2017	IVF	Age of 25 40 y; BMI of 19 35 kg/m^2; ≥2 failed fresh IVF/ICSI cycles followed by embryo transfer of at least 2 very good quality embryos on day 3; basal FSH level of ≤12 mIU/mL; absence of coagulation and/or autoimmune disorders	Previous IF (≥1)	230	LBR

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TABLE 1

Continued.

Interventions	Study	Country	Design	Duration	Population	Inclusion criteria	Subgroup	Total analyzed	Outcome
Corticosteroids	Bider et al. (1996) (49)	Israel	RCT	February 1993 to December 1994	IVF	FET; normal uterus; tubal occlusion; normal hormone profile; normal SFA	Good prognosis	99	LBR
	Bider et al. (1999) (48)	Israel	Retrospective cohort	Unstated	IVF	PCOS; irregular menstrual cycles; failure of clomiphene citrate or hMG/hCG treatment; LH/FSH ratio of >2; high DHEAS and testosterone levels	Good prognosis	71	LBR
	Litwicka et al. (2015) (51)	Italy	RCT	January 2011 to April 2012	IVF	Age of <40 y; BMI of 18 29 kg/m^2; thyroid autoimmunity; regular (21 35 days) menstrual cycles; presence of both ovaries; normal ovarian reserve; normal ovaries on ultrasound	Autoimmunity	60	LBR
	Moffitt et al. (1995) (50)	USA	RCT	January to September 1993	IVF	Unselected	Unselected	206	LBR
	Ozmen et al. (2018) (47)	Turkey	Retrospective cohort	January 2010 to June 2013	IVF	Age of 18 40 y; first IVF cycle only; normal baseline hormone profile; tubal or unexplained infertility; ICSI treatment	Good prognosis	964	LBR
	Turi et al. (2010) (52)	Italy	RCT	January 2006 to August 2008	IUI	Age of 20 38 y; positive antithyroid antibodies; ≤2 previous ART cycles; regular menstrual cycles of 24 35 days; BMI of 17 29 kg/m^2; no treatment with clomiphene citrate or gonadotropins within 1 month before the date of recruitment; normal uterine cavity; bilateral tubal patency	Autoimmunity	48	LBR
	van Kasteren et al. (1999) (53)	the Netherlands	RCT	Unstated	OI TI	Age of 18 40 y; idiopathic premature ovarian failure; normal karyotype; no history of radiotherapy or chemotherapy.	Low ovarian response	36	LBR
Aspirin plus corticosteroid	Revelli et al. (2008) (56)	Italy	RCT	October 2002 to April 2006	IVF	Age of ≤40 y; first IVF/ICSI cycle; only fresh embryo transfer cycles	Good prognosis	395	OPR
G CSF (intrauterine)	Eftekhar et al. (2016) (67)	Iran	RCT	March to September 2015	IVF	Age of 18 40 y; normal endometrial thickness	Good prognosis	113	OPR
	Huang et al. (2020) (68)	People's Republic of China	RCT	December 2015 to July 2017	IVF	Age of ≤38 y; BMI of 18 24 kg/m^2; primary infertility; previous IF (≥2); normal endometrial thickness (8 16 mm); 2 or more frozen embryos available	Previous IF (≥1)	104	LBR
	Jain et al. (2018) (69)	India	RCT	Unstated	IVF	Age of 21 38 y; BMI of 18.5 29.9 kg/m^2; normal hormone profile	Good prognosis	150	OPR
	Kalem et al. (2020) (70)	Turkey	RCT	March 2016 to December 2017	IVF	Age of <40 y; ≥3 previous IFs; FSH level of <15 mIU/mL	Previous IF (≥1)	173	LBR
	Kunicki et al. (2017) (65)	Poland	Prospective cohort	October 2011 to October 2014	IVF	Thin endometrium; FET; previously cancelled IVF due to thin endometrium (<7 mm); previous treatment of unresponsive endometrium with oral/vaginal estradiol, sildenafil citrate, or aspirin; lack of contraindications for G CSF treatment; own embryo FET	Thin endometrium	62	LBR
	Mao et al. (2020) (71)	People's Republic of China	RCT	March 2017 to May 2018	IVF	Age of 20 42 y; BMI of 20 28 kg/m^2; FET; regular menstrual cycles; normal hormone profile; thin endometrium (<7 mm) or mild to moderate intrauterine adhesions; no contraindications for G CSF treatment; no fibroids, polyps or PCOS; availability of at least 2 good quality embryos	Thin endometrium	304	LBR
	Xu et al. (2015) (66)	People's Republic of China	Prospective cohort	July 2012 to July 2013	IVF	Age of <40 y; FSH level of <10 IU/L; endometrial thickness of <7 mm; no uterine malformations; no contraindications for G CSF treatment	Thin endometrium	66	LBR

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TABLE 1

Continued.

Interventions	Study	Country	Design	Duration	Population	Inclusion criteria	Subgroup	Total analyzed	Outcome
G CSF (subcutaneous)	Arefi et al. (2018) (73)	Iran	RCT	May 2010 to October 2015	IVF	Age of 22 44 y, previous IF (>2)	Previous IF (≥1)	52	LBR
Intralipid	Al Zebeidi et al. (2020) (79)	Saudi Arabia	RCT	January 2015 to December 2016	IVF	Age of <42 y; BMI of <30 kg/m^2; 3 previous IFs; normal uterine cavity; normal hormone and lipid profile	Previous IF (≥1)	142	LBR
	Singh et al. (2019) (78)	India	RCT	January 2017 to January 2018	IVF	Age of 20 40 y; BMI of 20 32 kg/m^2; nondonor oocyte IVF; ≥1 previous IF; normal baseline hormonal profile; morphologically normal oocytes and embryos	Previous IF (≥1) and thin endometrium	102	LBR
IVIG	Ahmadi et al. (2017) (84)	Iran	Prospective cohort	February 2015 to March 2016	IVF	3 IFs; preconception Th1/Th2 ratio and NK cell frequency and activity elevation	Previous IF (≥1) and high inflammation	72	LBR
	Chernyshov et al. (2016) (85)	Ukraine	Prospective cohort	Unstated	IVF	Age of 23 35 y; RIF (≥3); good quality embryos and quantity	Previous IF (≥1)	238	LBR
	Ho et al. (2020) (86)	People's Republic of China	Prospective cohort	January 2007 to October 2011	IVF	RIF (≥2 previous failures) of unknown etiology	Previous IF (≥1)	283	LBR
	Moraru et al. (2012) (82)	Spain	Prospective cohort	May 2005 to May 2011	IVF	RIF (definition unstated); high NK or NK like cell level	Previous IF (≥1) and high inflammation	40	LBR
	Sher et al. (1998) (87)	USA	Prospective cohort	January 1992 to 1996	IVF	Age of <40 y; antithyroid antibodies; negative APL antibodies	Autoimmunity	82	LBR
	Stephenson and Fluker (2000) (88)	Canada	RCT	March 1995 to July 1998	IVF	Age of 18 44 y; ≥2 previous failed fresh or frozen embryo transfers resulting in IF, biochemical pregnancy loss, or clinical miscarriage at ≤8 weeks of gestation	Previous IF (≥1)	51	LBR
r LIF	Brinsden et al. (2009) (91)	UK	RCT	Unstated	IVF	Age of 21 37 y; 2 or more failed ART cycles; BMI of 20 30 kg/m^2; normal hormone profile; normal SFA	Previous IF (≥1)	150	LBR
PBMCs	Li et al. (2017) (95)	People's Republic of China	Unstated	July 2013 to March 2015	IVF	Previous IF (≥1)	Previous IF (≥1)	633	LBR
	Okitsu et al. (2011) (93)	Japan	Prospective cohort	May 2007 to February 2010	IVF	Previous IF (≥1)	Previous IF (≥1)	253	LBR
	Pourmoghadam et al. (2020) (96)	Iran	RCT	October 2017 to September 2018	IVF	Age of <45 y; BMI of <30 kg/m^2; previous IF (≥3); primary infertility; regular menstrual cycles; normal SFA	Previous IF (≥1)	100	LBR
	Yoshioka et al. (2006) (94)	Japan	Unstated	Unstated	IVF	Previous IF (≥4); normal ovarian reserve (FSH level of <15 mIU/mL)	Previous IF (≥1)	35	LBR
	Yu et al. (2016) (97)	People's Republic of China	RCT	September 2013 to May 2014	IVF	Age of <35 y; RIF (≥3); normal ovarian reserve (FSH level of <15 mIU/mL)	Previous IF (≥1)	212	LBR
Aspirin ± subcutaneous heparin	Akhtar et al. (2013) (21)	UK	Retrospective cohort	January 2005 to September 2010	IVF	Age of 23 44 y; previous failed implantation (≥1)	Previous IF (≥1)	206	LBR
	Kutteh et al. (1997) (22)	USA	Prospective cohort	June 1995 to August 1996	IVF	Age of <42 y; first IVF cycle; FSH level of <20 mIU/mL, estradiol level of <50 pg/mL; normal uterine cavity	Good prognosis	191	OPR
	Sher et al. (1994) (23)	USA	Cohort unstated	January 1992 to June 1994	IVF	Antiphospholipid antibody positivity; normal uterine cavity as observed by hysteroscopy	Autoimmunity	194	OPR
IVIG plus TNF α inhibitor	Winger et al. (2009) (83)	UK	Retrospective cohort	May 2003 to December 2006	IVF	Age of <38 y; elevated Th1/Th2 cytokine ratio before index fresh IVF cycle; negative tuberculin skin test; good embryo development (≥5 day 3 embryos with ≥5 cells)	High inflammation	75	LBR

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TABLE 1

Continued

Interventions	Study	Country	Design	Duration	Population	Inclusion criteria	Subgroup	Total analyzed	Outcome
LMWH (subcutaneous) plus corticosteroid	Fawzy and El-Refaeey (2014) (43)	Egypt	Prospective cohort	January 2008 to October 2012	IVF	Age of <39 y; failed previous 1 or 2 implantations; fresh ejaculate fertile sperm used for ICSI; no hormonal disorders; normal uterine cavity	Previous IF (≥ 1)	295	OPR
	Srisatidos et al (2018) (44)	Greece and Egypt	Retrospective cohort	February 2012 to July 2016	IVF	Age of <45 y; ≥ 2 failed IVF cycles; BMI of 19–35 kg/m^2; FSH level of ≤15 mIU/mL; absence of coagulation and/or autoimmune disorders	Previous IF (≥ 1)	115	LBR
TNF-α inhibitor	Onalan et al (2018) (98)	Turkey	Retrospective cohort (case-control analysis)	January 2014 to January 2015	IVF	Endometriomas	Good prognosis	66	LBR

Note: APL = antiphospholipid; ART = assisted reproductive technology; BMI = body mass index; DHEAS = dehydroepiandrosterone; FET = frozen embryo transfer; FSH = follicle-stimulating hormone; G-CSF = granulocyte colony-stimulating factor; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin; ICSI = intracytoplasmic sperm injection; IF = implantation failure; IU = international units; IVF = in vitro fertilization; IVIG = intravenous immunoglobulin; LBR = live birth rate; LH = luteinizing hormone; LMWH = low-molecular-weight heparin; NK = natural killer; OI = ovulation induction; OPR = ongoing pregnancy rate; PBMC = peripheral blood mononuclear cell; PCOS = polycystic ovary syndrome; RCT, =randomized controlled trial; r-hLF = recombinant human leukemia inhibitory factor; RIF = recurrent implantation failure; RPL = recurrent pregnancy loss; SFA = seminal fluid analysis; Th = T helper; TI = timed intercourse; TNF = tumor necrosis factor

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similar numbers in the heparin and no treatment/placebo groups (40, 41, 43, 44). Further trials are needed to determine whether patients with previous implantation failure and evidence of an acquired or inherited thrombophilia may benefit from LMWH.

CORTICOSTEROIDS

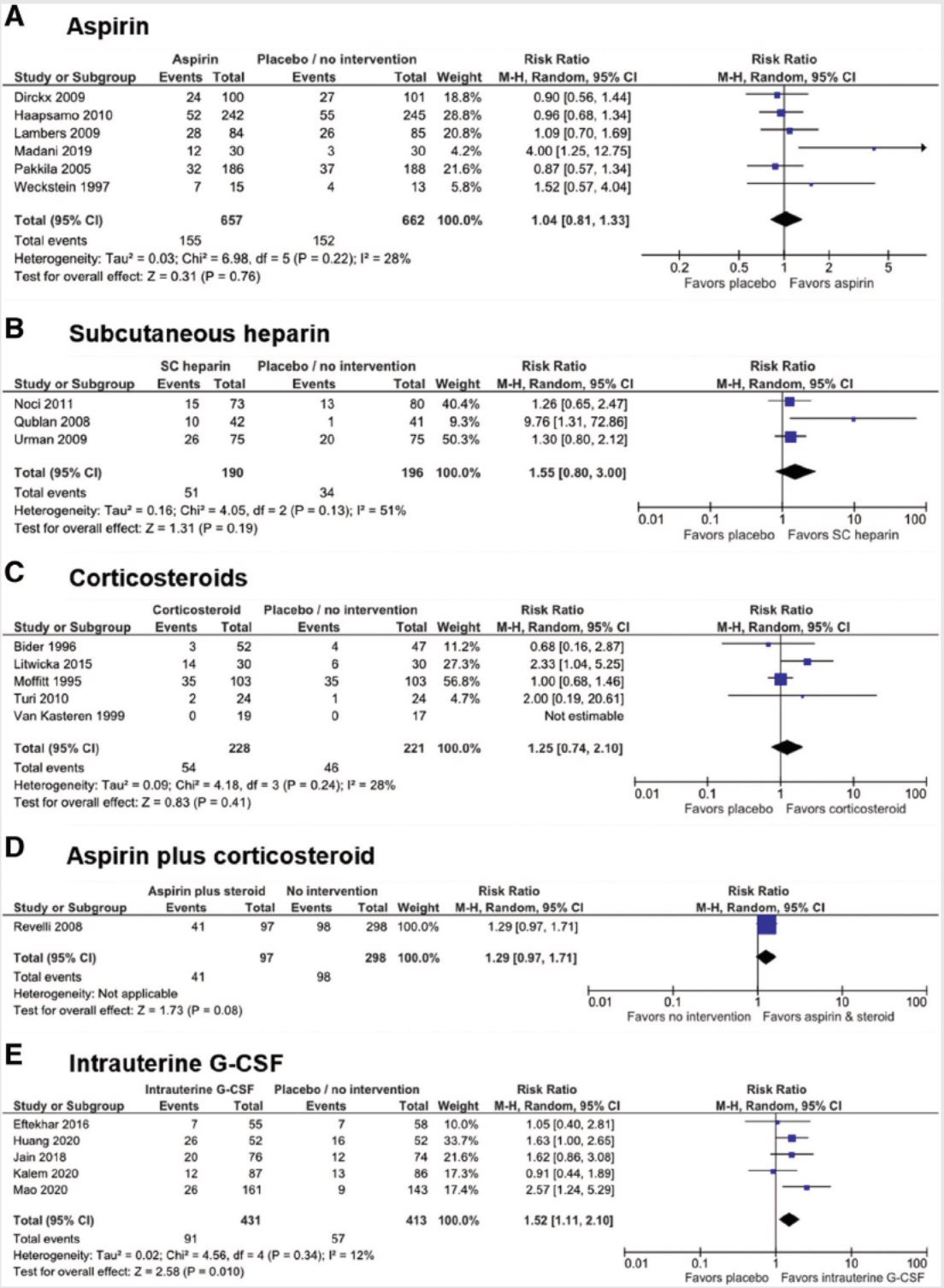
Corticosteroids have been widely used in the context of IVF treatment. It has been proposed that steroids may improve the uterine immune environment by either modulating the uterine NK cell count or activity or altering the endometrial cytokine environment (45, 46). We identified 2 nonrandomized studies that investigated the effect of corticosteroids vs. no intervention on the LBR; both reported uncertain findings for this outcome (47, 48) (Table 1). In addition, our meta-analysis of 5 RCTs including 449 patients investigating corticosteroids vs. placebo or no treatment showed no clear evidence of an increased number of ongoing pregnancies or live births (RR, 1.25; 95% CI, 0.74–2.10; 5 RCTs; $I^2 = 0$; low-certainty evidence) (49–53) (Fig. 1 and Table 2).

An additional rationale for the use of corticosteroids has been to improve outcomes for women with subfertility who have autoantibodies. However, studies investigating the association between subfertility and autoantibodies have shown varying results (54). Although a recent meta-analysis has failed to demonstrate an association between thyroid autoantibodies and poor outcomes in patients undergoing IVF or intracytoplasmic sperm injection (55), our subgroup analysis including solely women with positive antithyroid antibodies showed that treatment with corticosteroids may result in improved LBR (RR, 2.29; 95% CI, 1.07–4.94; 2 RCTs; $I^2 = 0$; low-certainty evidence). Notably, however, only 108 women participated in these studies, and in 1 publication, participants underwent intrauterine insemination, not IVF (52).

Corticosteroids are often prescribed in combination with other medications for women undergoing ART. We identified 1 RCT evaluating aspirin and corticosteroids vs. no intervention (56). The data were uncertain as to whether aspirin and corticosteroids in combination resulted in an increased OPR (RR, 1.29; 95% CI, 0.97–1.71; n = 395; low-certainty evidence) (Fig. 1 and Table 2).

Although generally considered to be safe in pregnancy, several studies have evaluated the possibility of teratogenicity with corticosteroid exposure. Initial evidence from the National Birth Defects Prevention Study in the United States suggested that corticosteroid exposure in the first trimester was associated with a significant, albeit small, increase in the risk of cleft lip and palate (57). However, more recent case-control data from the same registry including 1,577 children with cleft lip and palate no longer found this association (58). Adverse events reported from the trials included in this meta-analysis described typical effects of steroids, including insomnia and mild euphoria (53, 56). It is worth noting, however, that any use of corticosteroids beyond the first trimester of gestation should be restricted to women in whom the benefits are thought to outweigh the risks (e.g., asthma and autoimmune conditions). There is evidence suggesting that

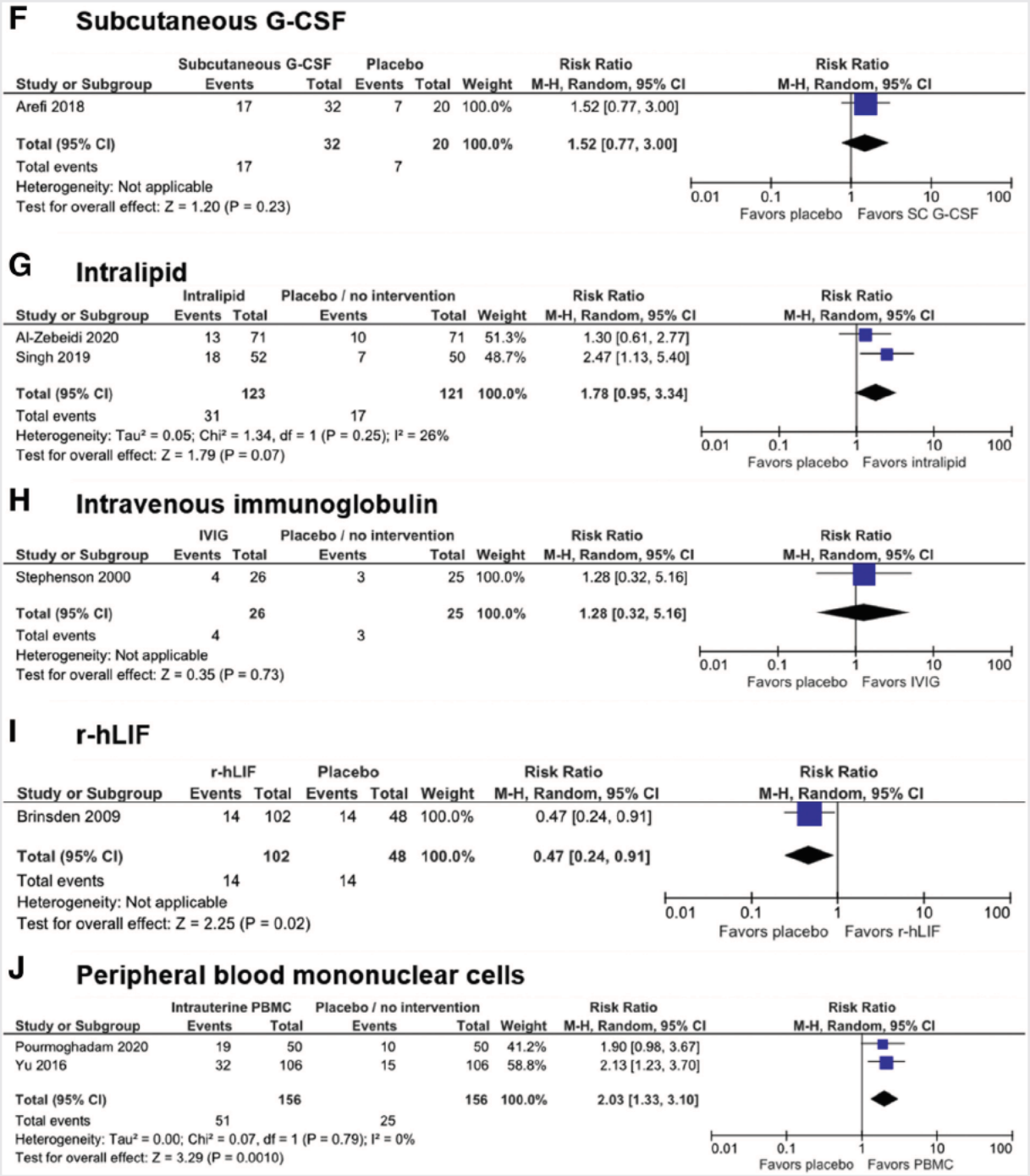
FIGURE 1



Meta analysis of randomized controlled trials investigating different immunologic therapies in comparison with placebo or no intervention on the rate of ongoing pregnancy or live birth in women with subfertility and/or undergoing assisted conception. CI confidence interval; df degrees of freedom; G CSF granulocyte colony stimulating factor; IVIG intravenous immunoglobulin; M H Mantel Haenszel test; PBMC peripheral blood mononuclear cell; r hLIF recombinant human leukemia inhibitory factor; SC subcutaneous.

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FIGURE 1



Continued

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TABLE 2

Summary of findings of included randomized controlled trials for the outcome of ongoing pregnancy or live birth.

	Anticipated absolute effects (95% CI)				
Intervention	**Risk with placebo or no intervention**	**Risk with intervention**	**Risk ratio (95% CI)**	**Number of participants (studies)**	**Certainty of the evidence (GRADE)**
Aspirin	230/1,000	239/1,000 (186 305)	RR, 1.04 (0.81 1.33)	1319 (6 RCTs)	⨁⨁⨁◯ Moderate[a]
Subcutaneous heparin	173/1,000	269/1,000 (139 520)	RR, 1.55 (0.80 3.00)	386 (3 RCTs)	⨁◯◯◯ Very low[a,b,c]
Corticosteroids	208/1,000	260/1,000 (154 437)	RR, 1.25 (0.74 2.10)	449 (5 RCTs)	⨁⨁◯◯ Low[a,b]
Aspirin plus corticosteroids	329/1,000	424/1,000 (319 562)	RR, 1.29 (0.97 1.71)	395 (1 RCT)	⨁⨁◯◯ Low[a,d]
Intrauterine G CSF	138/1,000	210/1,000 (153 290)	RR, 1.52 (1.11 2.10)	844 (5 RCTs)	⨁⨁◯◯ Low[a,b]
Subcutaneous G CSF	350/1,000	532/1,000 (269 1,000)	RR, 1.52 (0.77 3.00)	52 (1 RCT)	⨁◯◯◯ Very low[a,b,e]
Intralipid	140/1,000	250/1,000 (133 469)	RR, 1.78 (0.95 3.34)	244 (2 RCTs)	⨁◯◯◯ Very low[a,b,e]
IVIG	120/1,000	154/1,000 (38 619)	RR, 1.28 (0.32 5.16)	51 (1 RCT)	⨁⨁◯◯ Low[a,e]
r hLIF	292/1,000	137/1,000 (70 265)	RR, 0.47 (0.24 0.91)	150 (1 RCT)	⨁⨁◯◯ Low[a,e]
PBMCs	160/1,000	325/1,000 (213 497)	RR, 2.03 (1.33 3.10)	312 (2 RCTs)	⨁◯◯◯ Very low[a,b,e]

Note: Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
CI confidence interval; G-CSF granulocyte colony-stimulating factor; IVIG intravenous immunoglobulin; PBMCs peripheral blood mononuclear cells; RCT randomized controlled trial; r-hLIF recombinant leukemia inhibitory factor; RR risk ratio.
[a] Downgraded once for serious imprecision due to the low number of events and/or wide confidence intervals.
[b] Downgraded once for serious risk of bias in at least 1 of the included studies.
[c] Downgraded once for serious inconsistency due to high heterogeneity.
[d] Downgraded once for serious indirectness because the included study evaluated only participants with good prognosis, therefore limiting the applicability of its findings to subgroups.
[e] Downgraded once for serious indirectness because the included study or studies evaluated only participants with recurrent implantation failure, thus limiting the applicability of the findings to other subgroups.

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repeated antenatal exposure to corticosteroids is associated with obstetric complications (e.g., increased risk of infection) as well as mental and behavioral disorders in children (59–61).

Evidence from RCTs to date does not support the generalized use of steroids in improving the OPR or LBR in women undergoing assisted conception. However, some groups of patients, including those with autoantibodies or autoimmune disease, may benefit from steroid treatment (51). There is a need for large RCTs to better define the effectiveness of corticosteroids to improve outcomes in women with infertility.

GRANULOCYTE COLONY-STIMULATING FACTOR

Granulocyte colony-stimulating factor is a cytokine produced by multiple cell types, including endothelium, epithelium, monocytes, macrophages, and bone marrow cells. Granulocyte colony-stimulating factor primarily stimulates the proliferation and survival of neutrophils (62). Recombinant G-CSF has been shown in an ex vivo model to alter endometrial gene expression, potentially influencing endometrial remodeling, cellular adhesion pathways, and local endometrial immune modulation (63). Intrauterine G-CSF treatment for patients with a thin endometrium was first reported in 2011 (64), and there have since then been a number of studies investigating its efficacy in the context of IVF.

Two cohort studies did not observe a difference in the LBR (65, 66) in patients treated with intrauterine G-CSF. In addition, we identified 5 RCTs including 844 participants treated with intrauterine G-CSF or a placebo/no intervention (67–71) (Table 1). Intrauterine G-CSF may result in a higher OPR or LBR than placebo or no intervention (RR, 1.52; 95% CI, 1.11–2.10; $I^2 = 12\%$), although the certainly of the evidence was found to be low (72) (Fig. 1 and Table 2). A subgroup analysis of women with a thin endometrium treated with intrauterine G-CSF suggested that this is the group in whom the increase in the LBR is most substantial (RR, 2.57; 95% CI, 1.24–5.29; 1 RCT; n = 304), although the evidence was judged to be of low certainty owing to the serious risk of bias and low number of events.

Although fatigue and bone and muscle pain are common side effects of G-CSF treatment, very few adverse events were reported in the included studies investigating the use of intrauterine G-CSF, presumably because the systemic dose of G-CSF is very low after intrauterine instillation (66, 74, 75).

The effect of subcutaneous G-CSF during ART treatment cycles has also been investigated, although we identified no

TABLE 3

Summary of recommendations on the use of immunotherapies in assisted reproduction.

Intervention	ASRM	BFS	CFAS
Aspirin	"good evidence to recommend against the routine use of low dose aspirin to improve the outcome of live birth in ART cycles in the general population"	"lack of proven efficacy for routine use of aspirin as an adjuvant in IVF cycles"	"aspirin should not be routinely offered in RIF" "In patients with thin endometrium undergoing embryo transfer cycles, we suggest against the use of aspirin to improve pregnancy rates"
Heparin		"[the routine use of LMWH] in the wide population of women undergoing IVF treatment is not warranted" "[LMWH] should be carefully considered in women with thrombophilia"	"empirical LMWH for RIF should be limited to research settings"
Corticosteroids	"good evidence to recommend against the routine use of corticosteroids during stimulation [and the implantation window] to improve the outcome of live birth in ART cycles in the general population" Additional evidence required on the effectiveness of corticosteroids in subpopulations	"lack of robust evidence to support the routine use of corticosteroids empirically as an adjuvant in IVF cycles" "limited evidence that corticosteroids may improve pregnancy rates in women undergoing conventional IVF and in the subgroup of women with autoimmunity or unexplained implantation failure	"the use of glucocorticoids in RIF patients should be limited to research settings"
G CSF	"insufficient evidence to routinely recommend for or against G CSF administered locally or systemically to improve IVF outcomes"		"the use of G CSF in RIF patients should be limited to research settings" "in patients with thin endometrium undergoing embryo transfer cycles, we suggest against the use of intrauterine infusion of G CSF to improve pregnancy rates"
Intralipid	"insufficient evidence to routinely recommend intravenous fat emulsions for infertile women pursuing IVF" Additional evidence required on the effectiveness of intralipid in subpopulations	"lack of evidence to recommend intralipid infusion therapy as an adjuvant in IVF cycles. The use of intravenous lipids in this setting cannot therefore be supported"	"the use of intralipid in RIF patients should be limited to research settings"
IVIG	"insufficient evidence to recommend IVIG administration to improve IVF outcomes" Additional RCTs required to identify indications, risks, and benefits in subpopulations	"no convincing evidence for the use and safety of IVIg as adjuvants in women with recurrent implantation failure embarking on IVF. The use of IVIg in this setting cannot be supported"	"the use of immunotherapy in RIF patients should be limited to research settings"
r hLIF PBMCs	"insufficient evidence to recommend intrauterine infusion of autologous peripheral mononuclear cells before ET to improve IVF outcome"		
TNF α inhibitors	"insufficient evidence to recommend adalimumab treatment to improve IVF outcome"	"lack of evidence to indicate the effectiveness and safety of using anti TNF α agents as adjuvant in IVF cycles. The use of anti TNF α agents in this setting cannot therefore be supported"	

Note: ART assisted reproductive technology; ASRM American Society for Reproductive Medicine; BFS British Fertility Society; CFAS Canadian Fertility & Andrology Society; ET embryo transfer; G-CSF granulocyte colony-stimulating factor; IVF in vitro fertilization; IVIG intravenous immunoglobulin; LMWH low-molecular-weight heparin; PBMCs peripheral blood mononuclear cells; RCT randomized controlled trial; r-hLIF recombinant leukemia inhibitory factor; RIF recurrent implantation failure; TNF-α tumor necrosis factor alpha.

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cohort studies and only 1 RCT including 52 patients that reported no difference in the LBR (73). Given the limited therapeutic options for treating women who have a persistently thin endometrium, further good-quality studies are needed to assess the efficacy of G-CSF.

INTRALIPID

Intralipid is an intravenous fat emulsion containing soybean oil, egg phospholipid, glycerin, and water and is licensed for parenteral nutrition. Its proposed mechanisms of action in the context of subfertility is the suppression of NK cell activity and proinflammatory cytokines (76). Interestingly, a recent study by Foyle et al. (77) investigated whether intralipids may modulate the adaptive immune response in women. The investigators identified no evidence of significant alterations to T cell populations (albeit in the blood rather than in the endometrium) after intralipid infusion. However, intralipid resulted in changes to circulating plasma cytokines, which the investigators suggested have the potential to enhance endometrial receptivity.

Despite the common use of intralipids in clinical practice, we identified only 2 RCTs including 244 patients in which the pooled effect of intralipid on the LBR was uncertain (RR, 1.78; 95% CI, 0.95–3.34; $I^2 = 26\%$) (Fig. 1 and Table 2). In both studies, women had experienced previous failed implantation after ART (78, 79). Clearly, further evidence for the efficacy of intralipid is required before using this treatment in patients outside of a research setting. No serious adverse events were described in these articles, yet at higher doses, intralipid has been associated with increased risks of infection, venous thromboembolism, fat embolism, acute kidney injury, and allergic reactions (80).

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin is a pooled blood product licensed for several inflammatory and autoimmune conditions, such as chronic inflammatory demyelinating polyneuropathy, immune thrombocytopenia, and Kawasaki disease (81). We found a number of cohort studies assessing the effect of IVIG vs. no intervention. Most treated women considered to have high preconception Th1/Th2 ratios or a peripheral blood NK cell abnormality (82–84); others investigated participants who had previous implantation failure after ART treatment (85, 86), and 1 assessed IVIG use in women with antithyroid autoantibodies (87). Four of these studies found that treatment with IVIG led to a higher LBR (82, 84, 86, 87). The largest of these studies was a prospective analysis by Ho et al. (86) of 283 women with previous implantation failure (RR, 1.43; 95% CI, 1.05–1.95). In contrast, Chernyshov et al. (85) did not show a benefit to IVIG treatment, whereas the data from a retrospective cohort by Winger et al. (83) are difficult to interpret given multiple group comparators with a very small number of patients receiving no treatment. Despite the apparently encouraging results in some of these cohort studies, it is notable that we only identified 1 RCT evaluating 51 patients that demonstrated no clear effect of IVIG on the LBR (RR, 1.28; 95% CI, 0.32–5.16; low-certainty evidence) (88) (Fig. 1 and Table 2).

Intravenous immunoglobulin is commonly used as an adjuvant to ART, particularly in women with RIF or apparent immune dysregulation, despite the lack of high-quality evidence of a benefit in the OPR or LBR. Those studies that reported adverse events did not describe significant side effects (86, 88). In view of the positive data presented in several cohort studies, further large trials of this intervention are warranted, but the current evidence does not support routine clinical use in any specific patient population.

RECOMBINANT HUMAN LEUKEMIA INHIBITORY FACTOR

Leukemia inhibitory factor is a cytokine that was first identified as critical in mouse implantation (89). It has subsequently been investigated in humans, where it is expressed in the endometrium in the luteal phase of the menstrual cycle and thought to play a critical role in endometrial receptivity (90). Only 1 RCT has evaluated recombinant human leukemia inhibitory factor (r-hLIF) in a population of women with previous implantation failure undergoing ART (91). That study found that r-hLIF may result in a lower LBR (RR, 0.47; 95% CI, 0.24–0.91; n = 150; low-certainty evidence) (Fig. 1 and Table 2). This trial also reported more serious adverse events in the r-hLIF group, although the evidence was uncertain due to the relatively low numbers of patients in the study (RR, 4.24; 95% CI, 0.55–32.48; n = 150; low-certainty evidence). The apparent negative impact of r-hLIF on the LBR has undoubtedly discouraged others from further investigating this treatment.

PERIPHERAL BLOOD MONONUCLEAR CELLS

Peripheral blood mononuclear cells (PBMCs) include T and B lymphocytes, NK cells, as well as monocytes and dendritic cells. It has been hypothesized that intrauterine infusion of autologous PBMCs may enhance endometrial receptivity and improve the implantation rates. In most studies, PBMCs are cultured with human chorionic gonadotropin or corticotropin-releasing hormone before transfer (92). Some cohort studies have identified no difference in the LBR using intrauterine PBMCs (93), whereas others suggest an increase in the LBR (94). Most studies have investigated this treatment in patients with RIF, and 1 large cohort study demonstrated an increase in the LBR in participants with higher-order (≥ 4) implantation failure (95).

We identified 2 RCTs including 312 participants comparing intrauterine PBMC treatment with a placebo or no intervention that reported on the LBR (96, 97). In both studies, PBMCs were cocultured with human chorionic gonadotropin before transfer. Meta-analysis of these studies demonstrated a pooled RR of 2.03 (CI, 1.33–3.10; $I^2 = 0$) (Fig. 1), with anticipated absolute effects of achieving an LBR of 325 ongoing pregnancies or live births per 1,000 treated women compared with 160 patients receiving no treatment or placebo (Table 2). However, it must be noted that the certainty of the evidence was very low in these studies. Further, both trials investigated participants with previous implantation failure and, therefore, may not be generalizable to other subgroups of women with subfertility.

The putative mechanism of action of intrauterine PBMC therapy remains unclear. It is unlikely that the cells will breach the uterine mucosa, but in vitro culture of PBMCs activate cells and may stimulate the production of cytokines or factors beneficial to implantation (92). Endeavoring to identify which specific factors produced by cocultured PBMC may be ultimately more beneficial is the quest for studies investigating therapies for women with RIF.

TNF-α INHIBITORS

Tumor necrosis factor alpha is an inflammatory cytokine produced mainly by activated macrophages, T lymphocytes, and NK cells as well as nonimmune cells. Tumor necrosis factor alpha is synthesized within minutes of proinflammatory stress or injury, and chronic elevation of TNF-α levels is associated with several inflammatory conditions. Tumor necrosis factor alpha inhibitors are monoclonal antibody drugs licensed for the treatment of several of these conditions, including severe rheumatoid arthritis and other arthropathies, as well as inflammatory bowel disease. Some studies have described the ratios of Th1 and Th2 cytokines as being discordant or abnormal in the context of subfertility and RIF (8–10). This has led to the hypothesis that these medications may be beneficial, particularly in ART patients with RIF. Our systematic review identified no RCTs evaluating anti-TNF-α therapies on the OPR or LBR and found only 2 cohort studies where the data were expressed per participant (83, 98) (Table 1). In the study by Winger et al. (83), patients undergoing ART who were identified by the investigators as having an abnormal TNF-α/IL-10 ratio were administered adalimumab alone, IVIG alone, a combination of adalimumab and IVIG, or no treatment. The treatment was based on patient choice, and only 5 patients received no treatment. Although the investigators identified a higher LBR using the combination therapy than that in no treatment, the study design precludes drawing meaningful conclusions from these data. In another small retrospective study, Onalan et al. (98) evaluated the effectiveness of etanercept in women with endometrioma undergoing ART and found no difference in the LBR. Tumor necrosis factor alpha inhibitors should not be recommended to patients outside the context of a well-designed RCT. Most patients using this medication experience only mild side effects; however, biologic medications can result in more serious adverse events, such as an increased risk of severe infections (99).

CONCLUSION

Despite the widespread use of immunomodulatory drugs in clinical practice, this systematic review of the literature once again demonstrates a real lack of good-quality evidence for the use of immunologic treatments in women with subfertility or who are undergoing ART. In both research and clinical practice, patient selection remains controversial. Some clinicians administer immunologic therapies exclusively to women with known risk factors for implantation failure, for example, RIF or the existence of concomitant autoimmune conditions, such as antiphospholipid syndrome (100). Others apply less stringent criteria and use these drugs in the absence of known pathology that may impair implantation. Table 3 summarizes existing recommendations from different international societies on the use of immunotherapies in ART, highlighting that for most interventions, the evidence is scarce (101–104).

The use of immunologic treatments often accrues significant financial burden to patients and their partners (14, 105). Commonly prescribed drugs, such as aspirin and LMWH, are relatively inexpensive, yet the added cost of other immunotherapies can be substantial. For example, 1 injection of recombinant G-CSF solution (300 mcg) costs upward of US$360, with some centers administering more than 1 injection per treatment cycle (106, 107). Treatment with IVIG (approximately 1 g/kg) is even more expensive and can add up to US$6,000 to the cost of 1 ART cycle (108). It is also worth noting that IVIG is a blood product derived from the plasma of healthy donors and, thus, constitutes a finite resource (109). Clinicians have a duty to thoroughly counsel patients on the absence of conclusive evidence demonstrating a benefit of these therapies in women undergoing assisted conception.

Crucially, embryo aneuploidy represents the leading cause of implantation failure, abnormal implantation, and miscarriage, especially with advancing female age. In cases of embryo aneuploidy, the use of immunotherapy drugs remains futile (110). However, none of the included studies in this review restricted their samples to euploid embryos. There is a need for additional trials investigating immunomodulatory treatments in women having ART with embryos known to be chromosomally normal.

Recent studies have begun to elucidate the very complex cellular composition of the human endometrium and early decidua, including multiple subtypes of NK cells with distinctive immunomodulatory profiles (4, 111). In light of these data, current testing for immune dysfunction is likely to be far too simplistic. For example, the population of CD3+CD56+ endometrial cells identified and quantified by several clinical tests will in fact encompass a diverse range of cells, including subtypes of innate lymphoid cells and not just NK cells (112). Further, there is emerging evidence on various other etiologic pathways in RIF, including the role of killer immunoglobulin-like receptors/human leukocyte antigen incompatibility. However, our searches found no interventional studies evaluating the effectiveness and safety of immunotherapy drugs in such cases (113).

Despite the lack of certainty in the existing evidence, it would be premature to dismiss a future for immunologic treatments to improve outcomes for patients undergoing ART. Perhaps before embarking on major RCTs, clinicians and researchers need to agree on what pathology is being treated. The first challenge for the scientific community is to define tests that identify a true population of patients with an immune-mediated pathology and then undertake well-designed RCTs in suitably phenotyped patients who have the potential to benefit from immune treatments. In an era of personalized

medicine, there remain the scope and opportunity for reproductive immunology to improve outcomes for patients.

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CHAPTER 6: THESIS CONCLUSIONS

1. Introduction

This doctoral thesis contains a comprehensive body of research focusing on different aspects of ART, from ovarian stimulation to luteal phase support. I used various methodologies, including pairwise meta-analysis of RCTs and cohort studies, network meta-analysis, and prospective cohort analysis, to answer the questions originally presented in the introduction:

A. What is the relative effectiveness and safety of existing COS protocols?
B. What is the existing evidence on the association between serum progesterone levels and FET outcomes?
C. What is the effect of the route of progesterone administration on the association between serum progesterone levels and FET outcomes?
D. What is the current evidence on the effectiveness of immune therapies administered to women with subfertility and/or undergoing assisted conception?

This chapter summarises the main answers to each question, discusses the impact of the findings on clinical practice, and proposes unmet research needs to address in future studies.

2. What is the relative effectiveness and safety of existing COS protocols?

This question was answered by a Cochrane systematic review and network meta-analysis on COS (Chapter 2), including 326 studies and 57,541 women. We included 81 studies in

the primary quantitative synthesis of trials at low risk of selection and other biases, and 171 in our sensitivity analysis of all studies irrespective of bias risk.

Our primary findings reaffirm previous evidence that in women with predicted normal response, short GnRH antagonist protocols probably make little to no difference in live birth rate compared to long GnRH agonist protocols (69). Crucially, in this subgroup of women we confidently identified a 12% mean reduction in OHSS associated with the use of short antagonist protocols versus long agonist regimens (RR 0.88, 95% CI 0.78 to 0.99; moderate-certainty evidence). In addition, the sensitivity analysis including all studies showed similar findings for high-responding women. In this group, the reduction in OHSS with short antagonist protocols was even more pronounced (RR 0.61, 95% CI 0.48 to 0.78; moderate-certainty evidence), despite no evidence of a difference in live birth compared to long agonist protocols. These results constitute moderate-certainty evidence to support offering short antagonist protocols to women with predicted normal and high response, because of improved safety and non-inferior effectiveness.

The question of which COS protocol is most effective in women with predicted low response remains unanswered for the primary outcome of live birth. Nonetheless, it is important to note our low-certainty finding that short antagonist protocols may yield on average one fewer oocyte than long agonist protocols in this subgroup of women (MD -1.25, 95% CI -2.01 to -0.50). Furthermore, when comparing GnRH agonist flare protocols to long agonist regimens, the network evidence also favoured the latter, with nearly two fewer oocytes resulting from agonist flare protocols (MD -1.78, 95% CI -3.28 to -0.28, low-certainty evidence). This did not materially impact other clinically relevant outcomes, such

as ongoing pregnancy and live birth, owing to low participant numbers and study design limitations. However, such findings merit further investigation. Specifically, there is a need for well-designed, adequately-powered trials evaluating the impact of a higher number of oocytes on fresh and frozen embryo numbers, embryo ploidy status, and cumulative live birth rates. These outcomes are particularly pertinent in low-responding women, often with advanced age, in whom a higher number of oocytes may not necessarily translate into more euploid embryos.

This systematic review found that in women with predicted high response, hMG preparations probably result in a large reduction in OHSS compared to rFSH (RR 0.45, 95% CI 0.30 to 0.68). It is reasonable to postulate that such a reduction may result, at least partly, from the suggestion of a lower oocyte number following hMG administration in this subgroup of women (MD -2.16, 95% CI -3.59 to -0.74). Importantly, we did not confidently identify a difference in live birth for this comparison (RR 1.13, 95% CI 0.89 to 1.42), suggesting that a lower number of oocytes does not necessarily represent inferior quality. The mechanisms through which the addition of LH activity may impact follicle development in COS remain understudied (100). There is also uncertainty about how different FSH isoforms affect folliculogenesis and response to COS (35, 101). These results call for additional mechanistic studies on the pathways involved in follicle development in high-responding women.

We identified serious methodological flaws in nearly 48% of the studies included in this systematic review, precluding their addition to the meta-analyses. This led to substantially underpowered comparisons for many of the interventions and outcomes of interest.

Crucially, this signals the lack of well-conducted RCTs in reproductive medicine. Having undertaken a thorough assessment of design limitations, we found that nearly half of included studies failed to provide details of random sequence generation, and fewer than 1 in 3 adequately reported allocation concealment. Research suggests that inadequate or unclear sequence generation may overestimate effect sizes by 7%, whereas insufficient or unclear allocation concealment may exaggerate effect estimates by approximately 10% (102). Further, trials in reproductive medicine are particularly prone to a lack of transparency due to the complexities in reporting some of the outcomes. For example, reporting miscarriage rates per woman randomised may yield different results than using the number of cycles, embryo transfers or pregnancies as the denominator. Therefore, future reproductive medicine trials must follow well-established guidance for adequately reporting RCT methodology and outcomes (103, 104). Currently, the paucity of high-certainty evidence precludes any ranking of interventions, limiting the applicability of NMA findings.

Given the overwhelming scarcity of evidence for most comparisons, as shown by the summary of findings tables in this Cochrane review, there is a substantial unmet need for additional well-conducted RCTs evaluating COS protocols. In addition, better trials would improve the quality of systematic reviews, enabling women and clinicians to make informed choices based on moderate- and high-certainty evidence.

3. What is the existing evidence on the association between serum progesterone levels and FET outcomes?

This question was answered in Chapter 3, which detailed a systematic review and meta-analysis of 21 cohort studies evaluating the association between serum progesterone levels and treatment outcomes in FET cycles. The evidence showed that lower serum progesterone levels for thresholds below 10 ng/ml resulted in fewer live births and more miscarriages.

This systematic review strengthens the hypothesis that, similarly to natural menstrual cycles and fresh IVF cycles, some women undergoing FET using exogenous vaginal progesterone may exhibit LPD. These are important findings for various reasons.

Firstly, using serum progesterone to diagnose LPD in FET would be convenient and affordable. However, the existing studies have aimed to identify associations between serum progesterone and FET outcomes rather than diagnostic or prognostic accuracy. There remains a need to conduct validation studies of serum progesterone as a diagnostic tool for LPD. This would require additional data on reproducibility, reference standards, and evaluating assay precision and comparability (105, 106).

Secondly, identifying an association between low serum progesterone and FET outcomes potentially paves the way for a simple yet effective intervention. This has been demonstrated by studies in which additional exogenous progesterone (usually subcutaneously) led to non-inferior outcomes in women whose serum progesterone was low compared to normo-progestogenic women (107, 108). Nevertheless, these studies have important limitations, including substantial confounding by indication. Future studies

should randomise women with low serum progesterone undergoing FET to additional progesterone, either by increasing the original dose or supplementing it with an added route of administration, versus placebo or no intervention. Furthermore, it is important to note that subcutaneous progesterone is expensive and not readily available in the National Health Service (NHS) in the United Kingdom. Until evidence of categorical benefit emerges, it is unlikely that measuring progesterone, followed by luteal rescue with subcutaneous administration, will become available to couples having publicly funded FET cycles.

Lastly, the existing evidence focuses almost exclusively on HRT-FET using vaginal progesterone. There was a scarcity of studies investigating non-vaginal routes of progesterone administration and the effect of other FET regimens (e.g., natural cycle) on serum progesterone levels and treatment outcomes. Thus, we could not quantitatively synthesise evidence other than that derived from HRT-FET cycles using vaginal progesterone. There remains a need for high-quality studies investigating associations between serum progesterone levels and live birth in different FET regimens.

4. What is the effect of the route of progesterone administration on the association between serum progesterone levels and FET outcomes?

Chapter 4 (the ProFET study) answered the question of how different routes of administration may affect serum progesterone levels and, in turn, the probability of live birth in FET cycles. The ProFET study was the first prospective cohort investigating serum progesterone in FET in the United Kingdom (UK), and the first multicentre study of its kind internationally. Despite challenges associated with staff shortages and the deprioritisation

of fertility services during the COVID-19 pandemic, we achieved a sample size of over 400 participants.

The ProFET study identified an association between low serum progesterone levels (<10th centile, 7.8 ng/ml) and diminished adjusted probability of live birth, and a tendency for increased odds of miscarriage. ProFET offered important insight into how serum progesterone is associated with live birth by reaffirming previous associations, in addition to investigating progesterone levels as a continuous variable and elucidating the role of FET regimen and progesterone route on the probability of live birth.

This was a well-designed, prospectively registered study. It included unadjusted and adjusted analyses which accounted for important effect modifiers such as female age, BMI, and a plethora of confounders identified in the FET pathway (e.g., type of cycle, administration of exogenous progesterone, and route of administration). Overall, we confidently identified an association between low serum progesterone and worse treatment outcomes in an unselected population undergoing FET. Importantly, however, this association appeared to be non-linear, and identified important research questions that merit further investigation.

The finding that women having exclusively subcutaneous progesterone exhibited a bell-shaped association between serum progesterone and the adjusted probability of live birth warrants careful examination. The subcutaneous route appears to have driven a reduction in effectiveness as progesterone rose above the 60th centile in the totality of the cohort. We could not elucidate whether this was because there was truly a nefarious effect of excessive circulating progesterone upon implantation when administered subcutaneously.

In addition, the pharmacokinetics of subcutaneous progesterone suggest that its serum levels remain high for a relatively short period (6-8 hours), after which they may plummet (109-111). It is possible that by measuring serum progesterone too early (within 4-6 hours of administration), we falsely identified high progesterone levels that did not accurately reflect a hypoprogestogenic state that may have possibly ensued. This calls for future studies investigating the pharmacokinetics of subcutaneous progesterone in relation to FET outcomes and, importantly, invites caution in the exclusive use of subcutaneous progesterone for LPS in FET.

Another important result of the ProFET study was the near-linear association between serum progesterone and the probability of live birth in women having NC-FET without exogenous progesterone and HRT-FET with vaginal progesterone supplementation. This is particularly significant given recent evidence demonstrating the corpus luteum's crucial role in preventing gestational hypertensive disorders (GHD). Historically, trials have found a higher risk of GHD in frozen embryo transfer (FET) versus fresh cycles, although for unclear reasons (112). Recent data show that HRT-FET is specifically associated with at least a two-fold rise in preeclampsia risk versus NC-FET, and an increased risk of abnormally invasive placenta and gestational diabetes mellitus (113, 114). Such an increase may result from the absence of a corpus luteum in HRT-FET (115). From a research perspective, there is a need to elucidate the mechanisms through which the corpus luteum may facilitate healthy implantation, including the impact of specific luteal secretory products (e.g., relaxin, inflammation markers) (116). From a clinical standpoint, the proposed benefit of the corpus luteum in protecting against preeclampsia should prompt practitioners to re-evaluate HRT-FET cycles, possibly in favour of NC-FET in ovulatory women. Future studies

should investigate whether additional progesterone supplementation in hypoprogestogenic NC-FET cycles may offer a similar benefit to that of women having HRT-FET with vaginal progesterone while reducing the risk of late-pregnancy complications because of the presence of a corpus luteum.

The above considerations also highlight the importance of providing patients with evidence-based advice to enable informed choice. Lastly, they emphasise a wider need for better integration between fertility, early pregnancy and obstetric care, which would allow early referral of high-risk fertility patients to tertiary units for more vigilant monitoring in pregnancy.

5. What is the current evidence on the effectiveness of immune therapies administered to women with subfertility and/or undergoing assisted conception?

This question was answered by the systematic review and meta-analysis presented in Chapter 5, which has now been published. We included 27 RCTs and 26 cohort studies evaluating a total of fourteen treatment comparisons in 10,888 participants. Our primary qualitative and quantitative analyses identified variations in the effectiveness of different drugs, and most pairwise comparisons featured high uncertainty. However, the subgroup analyses showed that some of the included interventions might benefit selected women with specific baseline characteristics, including previous implantation failure and evidence of autoimmunity. Further studies are needed to strengthen the quality of the evidence.

The findings of this systematic review indicate that in the absence of underlying pathology (e.g., antiphospholipid syndrome), aspirin probably offers little to no benefit to live birth in

women undergoing IVF. Aspirin is a cheap and readily accessible drug. In the absence of significant evidence of harm, some women may opt to seek it while undergoing fertility treatment, although they should be counselled that this is probably ineffective and may lead to systemic side effects (e.g., gastrointestinal haemorrhage). For the remaining interventions, the evidence was either of low or very low certainty.

The main strength of this review was its comprehensiveness. We conducted extensive searches to identify eligible references, and included both randomised and non-randomised trials to evaluate the totality of interventional evidence on immunological therapies in women undergoing assisted conception. In addition, we limited our inclusion criteria to peer-reviewed manuscripts to ensure the extracted data had undergone scientific scrutiny prior to publication. We also restricted the included studies to articles where analyses had been performed per woman, further reducing the risk of bias in our conclusions.

This review was limited by the high degree of variation identified in the participants' characteristics, which hindered the generalisability of our findings. We were nonetheless able to classify women into subgroups and undertake meta-analyses according to patient profile, substantially reducing heterogeneity. In addition, many of the included studies evaluated participants who were deemed to have a good prognosis at the time of recruitment. In women without clear risk factors for treatment failure (e.g., thin endometrium or altered expression of endometrial cytokines), it is reasonable to postulate that using immunomodulatory drugs may have been futile. Larger, multicentre trials should focus on patient subgroups who may most benefit from immunomodulatory drugs (e.g.,

thrombophilia, previous implantation failure). Positive signals identified from cohort and existing RCTs in this review should inform future research on specific interventions in this field, including, for example, the suggestion of benefit from intrauterine G-CSF.

Lastly, we identified an overall lack of safety data, which should be considered a priority for interventional trials given the immunosuppressive nature of some of the interventions. This is particularly pertinent given recent data suggesting that the rate of true recurrent implantation failure may be lower than 5% when euploid blastocysts are transferred in three consecutive cycles (117). This should not dispute the crucial role of the endometrium in facilitating implantation, but invites careful reflection on whether the unselected use of potentially unproven adjuvants (e.g., transcriptomics assays, corticosteroids) may in fact exert a nefarious effect on reproductive outcomes (118).

6. Summary of thesis findings

Table 2. *Summary of thesis findings and structured answers for each thesis question.*

Chapter number	Population	Intervention	Comparison	Outcome(s)	Research design	Manuscript status
A. What is the relative effectiveness and safety of existing COS protocols?						
2	Women undergoing controlled ovarian stimulation for assisted conception (IVF and/or ICSI)	Controlled ovarian stimulation protocols	Any other controlled ovarian stimulation protocol	**Primary:** - Live birth - OHSS **Secondary:** - Clinical pregnancy - Ongoing pregnancy - Multiple pregnancy - Miscarriage - Ectopic pregnancy - Cycle cancellation - Oocyte number - Cleavage-stage embryo number - Blastocyst number - Number of cryopreserved embryos	Systematic review and network meta-analysis of randomised controlled trials	Accepted
Summary of findings: • **In women with predicted normal and high response, short GnRH antagonist protocols probably reduce OHSS by 12% and 39%, respectively, while resulting in little to no difference in live birth compared to long GnRH agonist protocols.** • **In women with predicted high response undergoing short GnRH antagonist protocols, ovarian stimulation with hMG probably reduces OHSS by 55% without compromising live birth rates.**						

Chapter number	Population	Intervention	Comparison	Outcome(s)	Research design	Manuscript status
B. What is the existing evidence on the association between serum progesterone levels and FET outcomes?						
3	Women undergoing FET treatment	Optimum serum progesterone, as identified by the investigators	Serum progesterone outside the optimum range	**Primary:** - Live birth or ongoing pregnancy (composite) **Secondary:** - Clinical pregnancy - Miscarriage - Adverse events attributable to exogenous progesterone	Systematic review and meta-analysis of observational studies	Published
Summary of findings: • **For serum progesterone thresholds below 10 ng/ml, women with serum progesterone above the specified cut-off experienced 47% more live births and 38% fewer miscarriages than women with progesterone levels lower than the cut-off.**						
C. What is the effect of the route of progesterone administration on the association between serum progesterone levels and FET outcomes?						
4	Women undergoing FET treatment	NA		**Primary:** - Live birth **Secondary:** - Implantation - Biochemical pregnancy - Clinical pregnancy - Miscarriage - Ectopic pregnancy	Multicentre observational prospective cohort study	Published

Chapter number	Population	Intervention	Comparison	Outcome(s)	Research design	Manuscript status
Summary of findings: • **In an unselected sample of women undergoing FET, serum progesterone below 7.8 ng/ml was associated with a 59% reduction in the adjusted odds of live birth, a 64% reduction in clinical pregnancy, and a trend towards an increase in miscarriage rates.** • **Women undergoing HRT-FET with exogenous vaginal progesterone or NC-FET exhibited a near-linear association between serum progesterone levels and the adjusted probability of live birth.** • **Women undergoing HRT-FET with subcutaneous progesterone exhibited a bell-shaped association between the mean serum progesterone levels and the adjusted probability of live birth.** • **Women undergoing HRT-FET with combined vaginal and subcutaneous progesterone experienced little variation in the mean probability of live birth as serum progesterone levels increased.**						
D. What is the current evidence on the effectiveness of immune therapies administered to women with subfertility and/or undergoing assisted conception?						
5	Women with subfertility and/or undergoing assisted conception	Immune therapies	Any other immune therapies, placebo, sham procedure or no intervention	**Primary:** - Live birth	Systematic review and meta-analysis of randomised controlled trials and interventional cohort studies	Published
Summary of findings: • **Aspirin probably results in little to no difference in live birth in women undergoing assisted conception.** • **Intrauterine G-CSF may improve the live birth rate by approximately 52%.** • **r-hLIF may reduce the live birth rate by approximately 53%.** • **The following interventions may result in little to no difference in live birth: corticosteroids, combined aspirin with corticosteroids, and IVIG.** • **The evidence is very uncertain about the effect of the following interventions: subcutaneous G-CSF, intralipid and PBMCs.**						

Abbreviations: COS, controlled ovarian stimulation; FET, frozen embryo transfer; G-CSF, granulocyte-colony stimulating factor; GnRH, gonadotrophin-releasing hormone; HRT, hormone replacement therapy; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation; IVIG, intravenous immunoglobulin; NA, not applicable; NC, natural cycle; OHSS, ovarian hyperstimulation syndrome; PBMCs, peripheral blood mononuclear cells; r-hLIF, recombinant human leukaemia inhibitory factor.

7. Conclusion

Since its inception in the 1970s, ART has led to the birth of millions of children worldwide, and this number continues to rise steeply. Unfortunately, such success constitutes the tip of an iceberg of failures, with fewer than 1 in 3 people undergoing ART achieving a live birth worldwide. This thesis has delved into various aspects of ART treatment, presenting high-quality evidence on strategies to improve success at multiple stages of an IVF cycle. Some of the findings in this thesis have now been used to effect change in clinical practice, and inspired further research in the field of reproductive medicine. The author hopes this work continues to help patients struggling with infertility, and that assisted conception practitioners consider it a helpful reference tool to inform clinical practice.

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APPENDICES

Appendix 1: Protocol registration record (PROSPERO) for "Serum progesterone in women undergoing frozen embryo cycles in assisted conception: a systematic review and meta-analysis" (Chapter 3)

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Systematic review

A list of fields that can be edited in an update can be found here

1. [12*changes] Review title.

Give the title of the review in English

Serum progesterone in women undergoing frozen embryo cycles in assisted conception: a systematic review and meta-analysis

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

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17/11/2019

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31/12/2020

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The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.
Review manuscript in development.

Review manuscript in development.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Pedro Melo

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Melo

7. * Named contact email.

Give the electronic email address of the named contact.

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Institute of Metabolism and Systems Research - University of Birmingham

Organisation web address:

https://www.birmingham.ac.uk/research/activity/metabolism-systems/index.aspx

11. * Review team members and their organisational affiliations.

[11.change]

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr Pedro Melo. Institute of Metabolism and Systems Research - University of Birmingham
Professor Arri Coomarasamy. Institute of Metabolism and Systems Research - University of Birmingham
Dr Yealin Chung. Institute of Metabolism and Systems Research - University of Birmingham
Mrs Oonagh Pickering. Institute of Metabolism and Systems Research - University of Birmingham
Dr Malcolm Price. University of Birmingham
Professor Simon Fishel. CARE Fertility
Dr Mohammed Khairy. CARE Fertility
Professor Charles Kingsland. CARE Fertility
Dr Philip Lowe. CARE Fertility
Dr Georgios Petsas. CARE Fertility
Dr Madhurima Rajkhowa. CARE Fertility
Dr Victoria Sephton. CARE Fertility
Dr Amanda Tozer. CARE Fertility
Dr Simon Wood. CARE Fertility
Dr Elena Labarta. IVI-RMA Valencia
Dr Mark Wilcox. CARE Fertility
Dr Adam Devall. University of Birmingham
Dr Ioannis Gallos. University of Birmingham

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

No funding sources will be involved in this project.

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

[13.change]

List actual or perceived conflicts of interest (financial or academic).

Yes

E.L. was the lead author in two of the manuscripts in this review (Labarta et al., 2017; and Labarta et al., 2021). She has additionally received a grant from Ferring in 2020, has provided consultancy services for MSD and Ferring Pharmaceuticals and is part of the Ferring Pharmaceuticals LIFE program and Merck Global program for Fertility Innovation Leaders. During the past 12 months, E.L. has received honoraria from Angelini/IBSA, Gedeon Richter and Ferring Pharmaceuticals for lecturing. M.W. reports personal fees from Ferring Pharmaceuticals, outside the submitted work.

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Is there an optimal level of serum progesterone associated with increased chance of live birth and reduced risk of miscarriage in women undergoing assisted conception with frozen embryo cycles?

16. Searches

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

From inception to November 2019: MEDLINE, PubMed, CINAHL, EMBASE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, ClinicalTrials.gov and grey literature (not widely available). We will apply no language restrictions to any of our searches.

Update June 2021: The review searches were updated on 4 September 2020 and 15 March 2021, using the same strategy that had been originally undertaken for the November 2019 searches.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Infertility is common, affecting 1 in 6 couples. Assisted reproductive technology (ART) involves the manipulation of gametes and embryos outside the human body with a view to achieve a pregnancy by replacing developing embryos into the uterine cavity. In recent years, there has been a shift towards a single embryo transfer to avoid the risks associated with multiple pregnancy. A surplus of embryos may therefore result from an in vitro fertilisation (IVF) cycle, and couples may opt to cryopreserve these for future embryo transfers. A receptive endometrium is essential for the success of ART, and this depends largely on adequate levels of progesterone. In a frozen-thawed embryo cycle with hormone replacement therapy (HRT), the endometrium is primed by administering exogenous oestrogen and progesterone, resulting in a thicker and more receptive endometrial epithelium. Nevertheless, protocols vary between institutions, and studies investigating the relationship between serum progesterone levels and pregnancy outcomes have yielded conflicting results. In addition, many women who have regular menstrual cycles opt to undergo FET without exogenous hormones (Natural cycle FET). There is a need for summarising existing evidence to

further inform current practice and identify potential areas for intervention with a view to improve outcomes in ART.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

We will include all women undergoing frozen-thawed IVF cycles whose serum progesterone levels have been measured at any point from ovulation (in a natural cycle) or commencement of exogenous progesterone supplementation (in a hormone replacement therapy cycle) to the first pregnancy test.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

This will be a systematic review of observational studies investigating the correlation between serum progesterone levels and pregnancy outcomes in women undergoing FET.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Our systematic review aims to summarise how "high" and "low" progesterone levels correlate with pregnancy outcomes. Where applicable, we will also perform an analysis of optimal ranges or intervals of progesterone levels linked to the highest live birth rates.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Observational - cohort and case-control studies.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The primary outcome of interest was the live birth rate per participating woman, defined as the delivery of a live fetus after 22 completed weeks of gestational age (Zegers-Hochschild et al, 2017).

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

As per timeline of individual studies.

25. Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Secondary outcomes included the clinical pregnancy rate, defined as the presence of one or more gestational sacs on ultrasound; the miscarriage rate, defined as the spontaneous loss of an intrauterine pregnancy prior to 22 completed weeks of gestation; the ectopic rate, defined as a pregnancy outside the uterine cavity as diagnosed by ultrasound, surgical identification or histopathology (Zegers-Hochschild et al, 2017); and the rate of adverse events attributable to exogenous progesterone supplementation (e.g. abdominal pain, bloating, nausea, depression and headache).

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

As per timeline of individual studies.

26. Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

We will include studies investigating the relationship between serum progesterone levels around the time of frozen embryo transfer (from ovulation in a natural cycle, or commencement of progesterone supplementation in a HRT cycle) and pregnancy outcomes. Due to variation in existing hormone replacement therapy (HRT) regimens for endometrial preparation and differences in study protocols, we will include papers where serum progesterone levels were measured any time from ovulation or the onset of exogenous progesterone supplementation (by any route available) to the first pregnancy test following embryo transfer. Studies performed in fresh cycles will be excluded.

Two independent reviewers will carry out the study selection, first by assessing titles and then by screening the abstracts of selected citations. The full manuscripts of studies that are deemed likely to meet our eligibility criteria will be obtained. Where reviewers disagree on study eligibility, this will be resolved by discussion with a third author.

The main data to be obtained will be the following:

- Authors
- Country of origin
- Study design
- Aim and intervention

- Population
- Inclusion criteria
- Exclusion criteria
- Number of participants (n)
- Age
- Progesterone route of administration (PV, PR, IM, SC)
- Data analysis - progesterone cut-off values (high vs low; or interval analysis)
- Miscarriage rate, clinical pregnancy rate, live birth rate (all per participant and, where applicable, per pregnancy)
- Conclusions

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

All articles meeting the selection criteria will undergo quality assessment using the Newcastle-Ottawa scale for quality assessment of observational studies (Wells et al, 2000).

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

All data analyses will be performed using Review Manager 5.3 (The Cochrane Collaboration, 2014). We will identify progesterone level cut-offs and divide available data into "high" and "low" progesterone. We will then meta-analyse the available data to determine the overall effect of high and low progesterone levels on pregnancy outcomes as detailed above. Our results will be summarised pictorially by using forest plots where applicable.

Two researchers will be involved in the data analysis and discrepancies will be resolved by discussion and, where needed, involvement of a third, supervising researcher.

Specifically:

- we will analyse outcome data (clinical pregnancy, live birth and miscarriage rates) according to high versus low progesterone
- where studies present data based on interval progesterone levels instead of progesterone levels described continuously, we will a. present the data in a separate table and b. ascertain whether there are optimal progesterone levels for pregnancy outcome (i.e., identify whether excessive serum progesterone may also be detrimental to pregnancy outcome)

- data on live birth rate, clinical pregnancy rate and miscarriage rate will be synthesised according to high versus low progesterone using risk ratios

- risk ratios for individual studies will be combined using a fixed-effects meta-analysis model

Update June 2021: In addition to preliminary analyses using Review Manager 5.3, the final analyses were performed using Stata Statistical Software (Release 16, TX, USA).

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

We will analyse data subsets according to the route of progesterone administration (oral, subcutaneous, intramuscular, vaginal or rectal).

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic

Yes

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
Yes

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care

No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

England

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

We plan to publish the results of this systematic review in a high impact journal.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Frozen embryo transfer, progesterone, infertility, assisted reproductive technology

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. Current review status.

[2. Changes]

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Completed_published

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

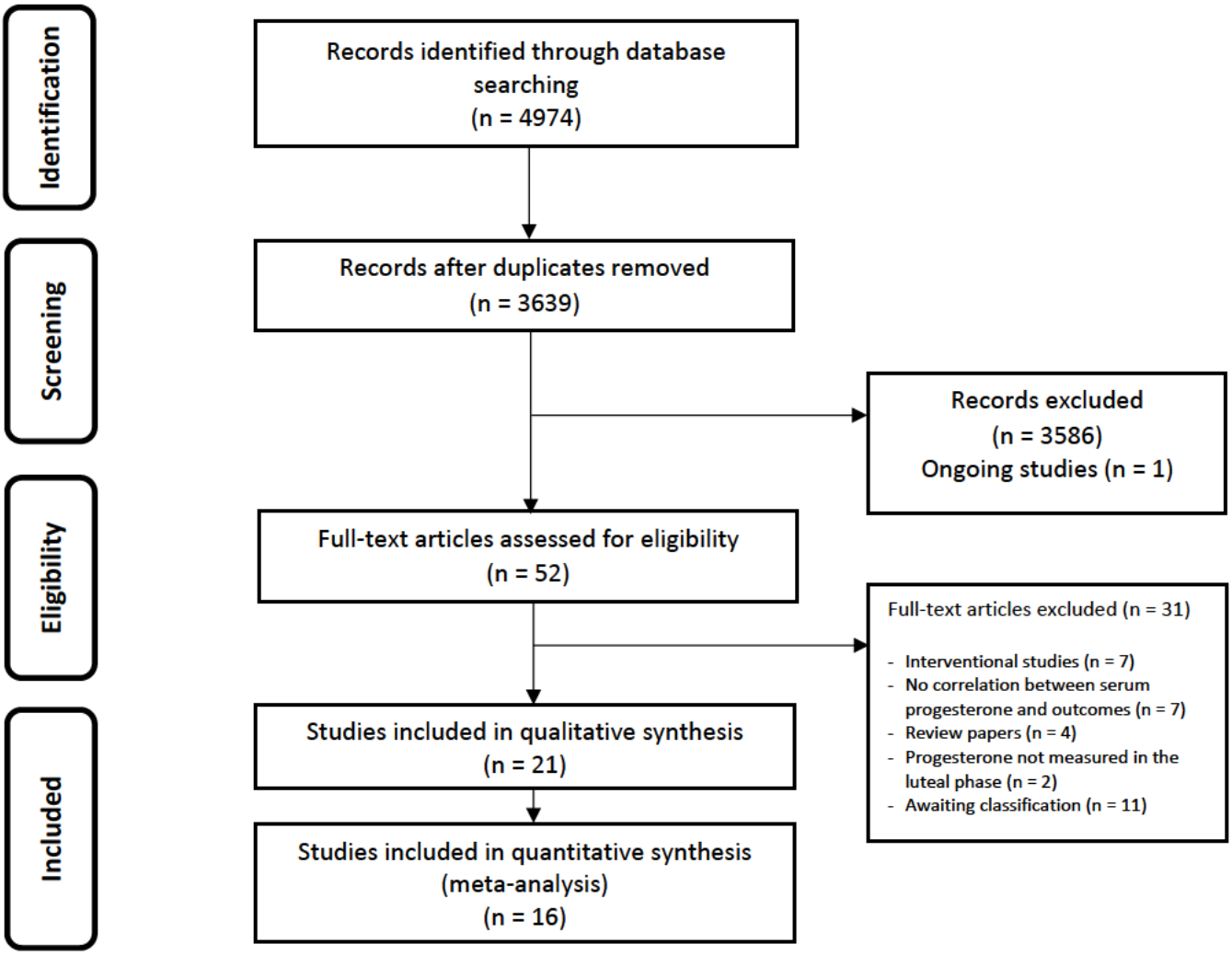
[1. Details]

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

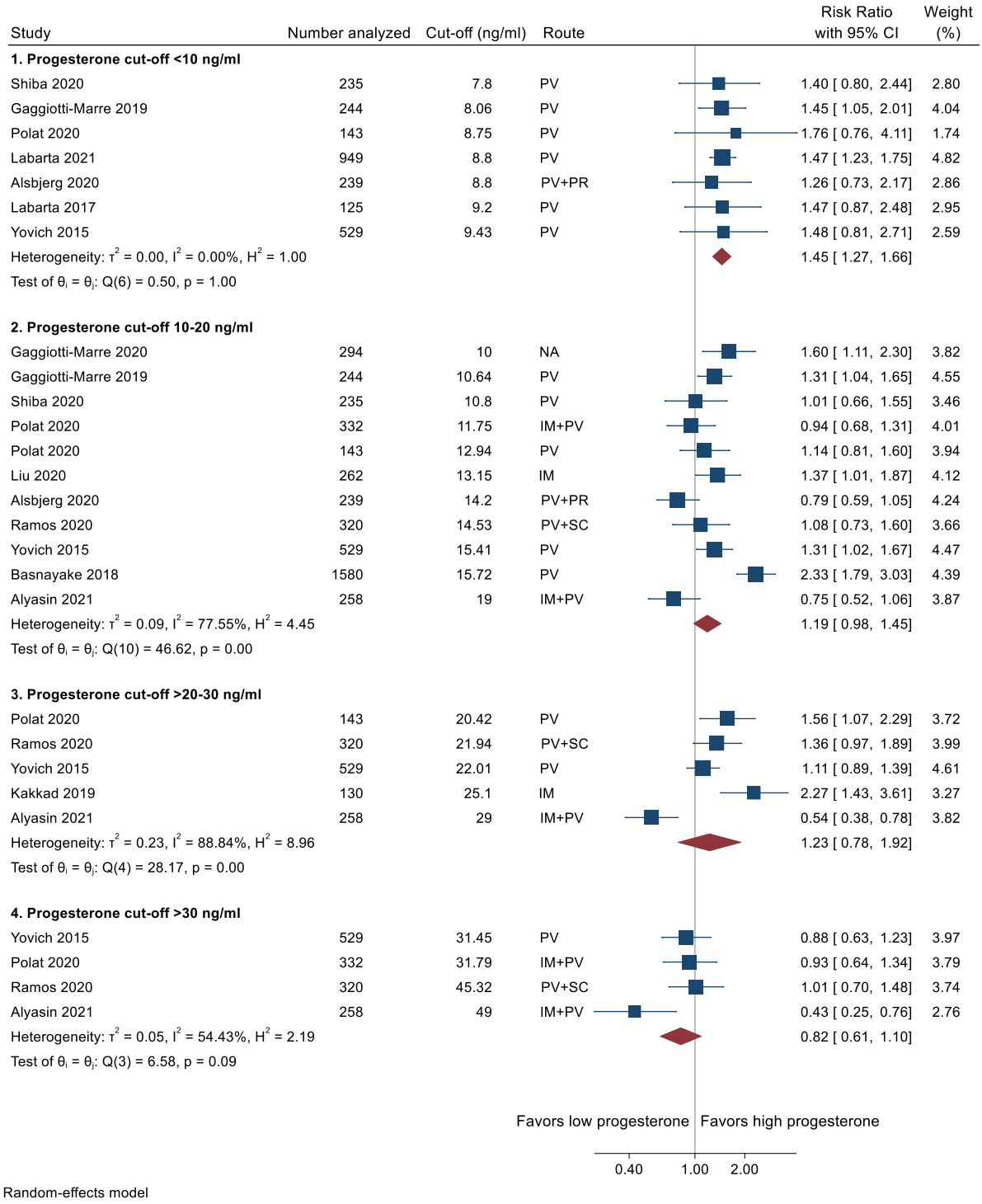
https://www.ScienceDirect.com/science/article/pii/S001502822100577X?dgcid=author

Give the link to the published review or preprint.

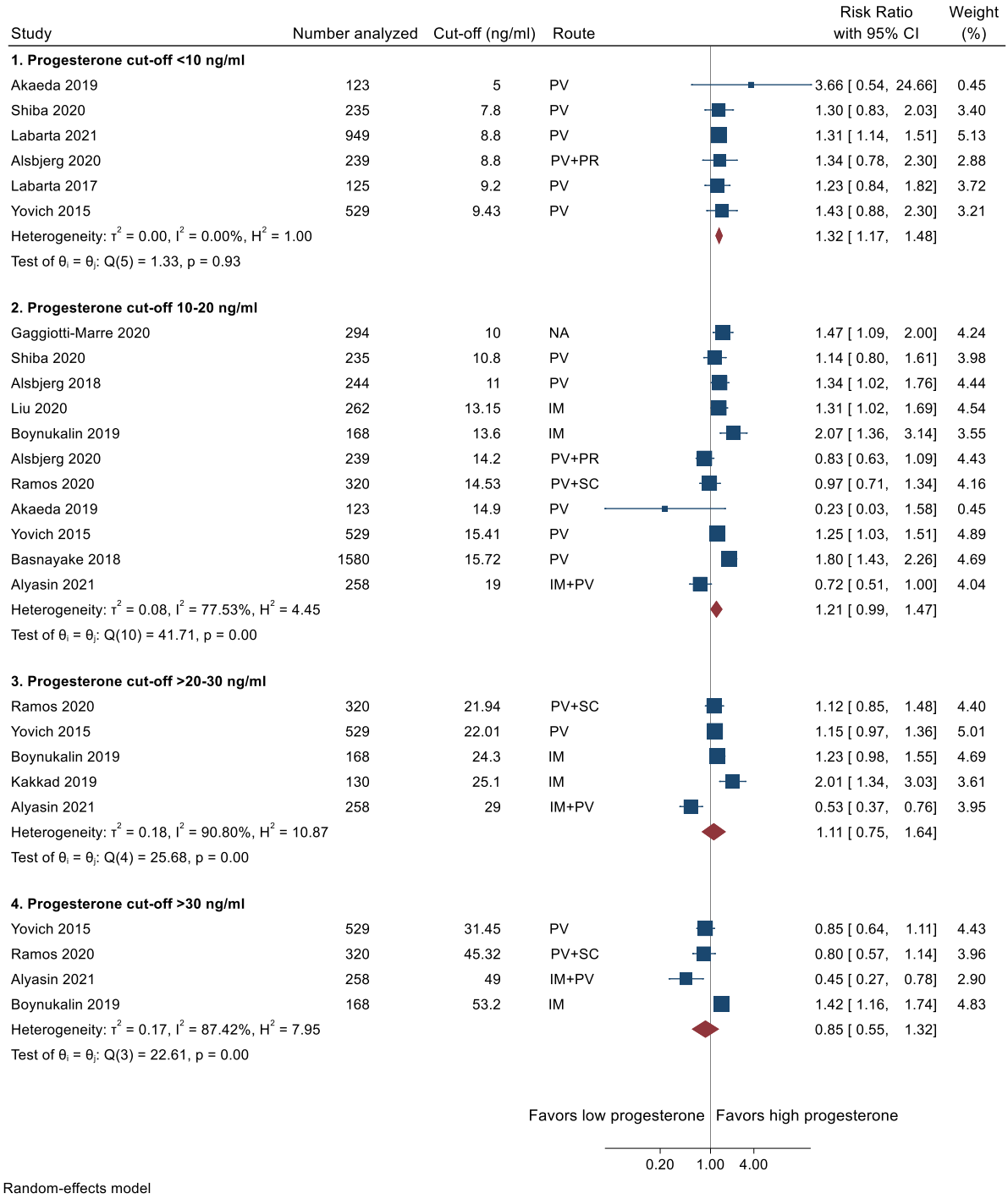
Appendix 2: Supplemental files for "Serum luteal phase progesterone in women undergoing frozen embryo transfer in assisted conception: a systematic review and meta-analysis" (Chapter 3)



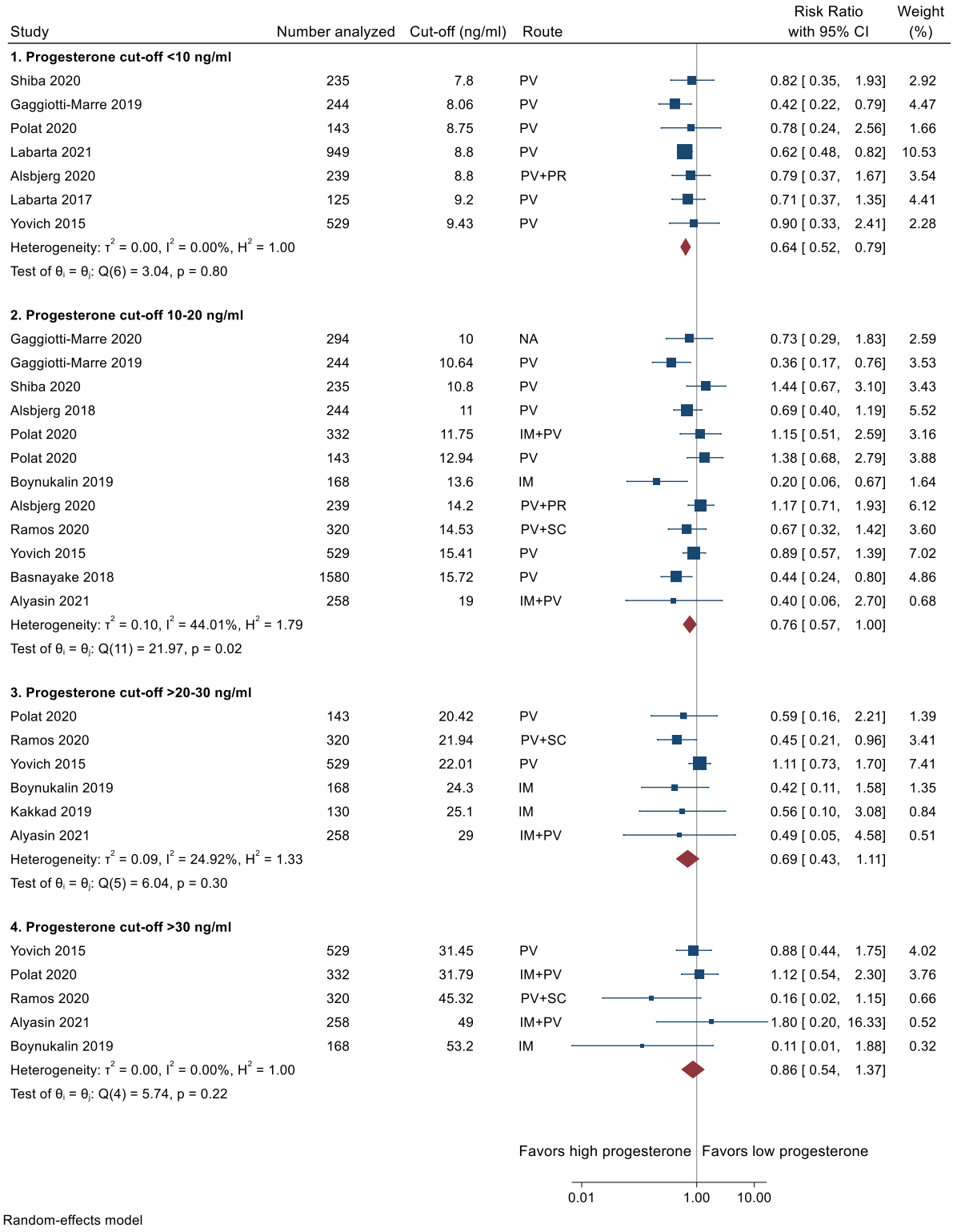
Supplemental Figure 1. Flow diagram of study selection process.



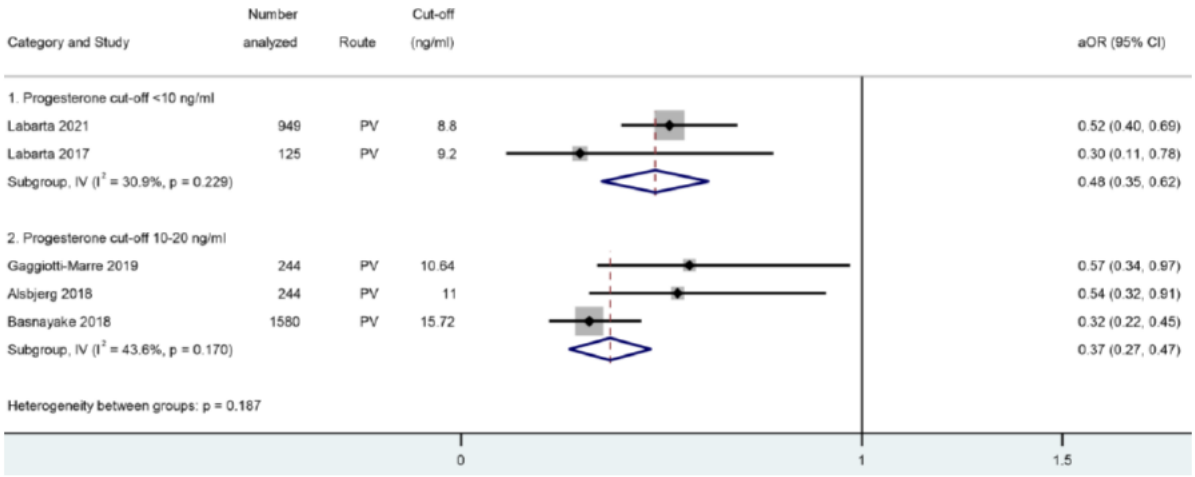
Supplemental Figure 2. Forest plot describing the association between different threshold categories of serum progesterone and ongoing pregnancy or live birth rates for women undergoing frozen embryo transfer cycles. Sensitivity analysis including all studies suitable for meta-analysis. CI, confidence interval; IM, intramuscular route; NA, not applicable (natural cycle); PR, rectal route; PV, vaginal route; SC, subcutaneous route.



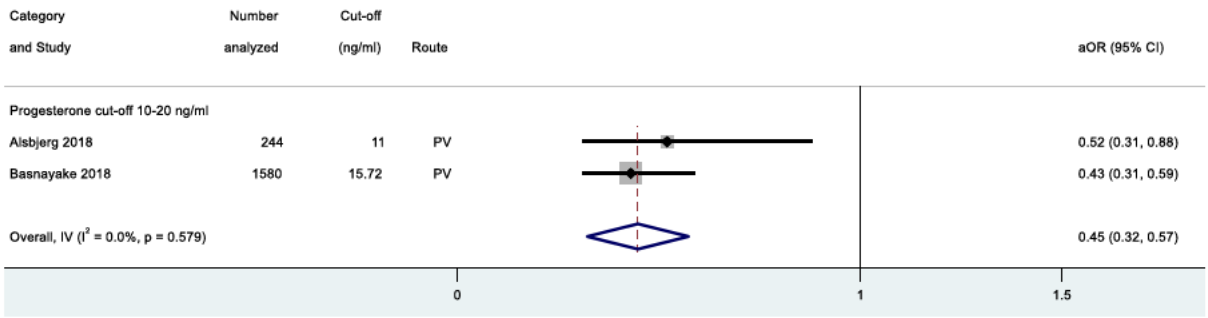
Supplemental Figure 3. Sensitivity analysis describing the association between different threshold categories of serum progesterone and clinical pregnancy rates for women undergoing frozen embryo transfer cycles. Sensitivity analysis including all studies suitable for meta-analysis. CI, confidence interval; IM, intramuscular route; NA, not applicable (natural cycle); PR, rectal route; PV, vaginal route; SC, subcutaneous route.



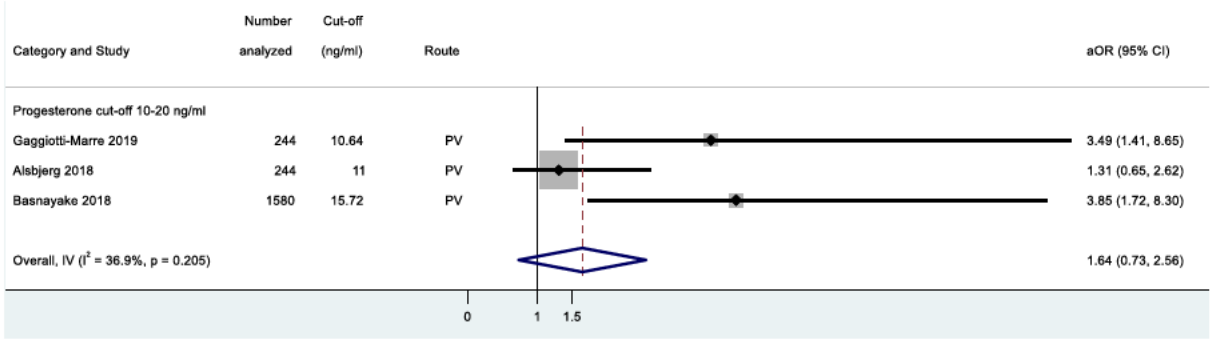
Supplemental Figure 4. Sensitivity analysis describing the association between different threshold categories of serum progesterone and miscarriage rates for women undergoing frozen embryo transfer cycles. Sensitivity analysis including all studies suitable for meta-analysis. CI, confidence interval; IM, intramuscular route; NA, not applicable (natural cycle); PR, rectal route; PV, vaginal route; SC, subcutaneous route.



Supplemental Figure 5. Meta-analysis describing the pooled adjusted effect of low serum progesterone (below specified cut-off) versus high serum progesterone (above specified cut-off) on ongoing pregnancy or live birth rates in women undergoing FET. aOR, adjusted odds ratios; CI, confidence interval; FET, frozen embryo transfer; IV, inverse variance; PV, vaginal route.



Supplemental Figure 6. Meta-analysis describing the pooled adjusted effect of low serum progesterone (below specified cut-off) versus high serum progesterone (above specified cut-off) on clinical pregnancy rates in women undergoing FET. aOR, adjusted odds ratios; CI, confidence interval; FET, frozen embryo transfer; IV, inverse variance; PV, vaginal route.



Supplemental Figure 7. Meta-analysis describing the pooled adjusted effect of low serum progesterone (below specified cut-off) versus high serum progesterone (above specified cut-off) on miscarriage rates in women undergoing FET. aOR, adjusted odds ratios; CI, confidence interval; FET, frozen embryo transfer; IV, inverse variance; PV, vaginal route.

Supplemental Table 1. Characteristics of excluded studies.

Author, year	Journal	Title	Reason for exclusion
Alsbjerg et al. (2020)	Journal of Assisted Reproduction and Genetics	Serum progesterone levels on day of embryo transfer in frozen embryo transfer cycles-the truth lies in the detail	Commentary paper
Alur-Gupta et al. (2020)	Fertility Research and Practice	Measuring serum estradiol and progesterone one day prior to frozen embryo transfer improves live birth rates	Interventional study
Cédrin-Durnerin et al. (2019)	Reproductive BioMedicine Online	Serum progesterone concentration and live birth rate in frozen–thawed embryo transfers with hormonally prepared endometrium	Interventional study
Chang et al. (2019)	Human Reproduction (conference abstract)	Can post-hoc progesterone supplementation rescue the clinical outcomes in the patients with low serum progesterone on the day of embryo transfer?	Interventional study
Commissaire et al. (2020)	Gynécologie Obstétrique Fertilité & Sénologie	Progesterone and frozen-thawed embryo transfer after hormonal replacement therapy for endometrial preparation: An update on medical practices	Review paper
Enatsu et al. (2018)	Reproductive medicine and biology	Effectiveness of high-dose transvaginal progesterone supplementation for women who are undergoing a frozen-thawed embryo transfer	Interventional study
Griesinger et al. (2007)	Human Reproduction	Mid-cycle serum levels of endogenous LH are not associated with the likelihood of pregnancy in artificial frozen-thawed embryo transfer cycles without pituitary suppression	Progesterone measured before the luteal phase
Irianni et al. (1992)	Human Reproduction	Influence of number of pre-embryos transferred, progesterone level and oestradiol/progesterone ratio at thaw on pregnancy results during replacement of cryopreserved pre-embryos in natural cycles	Progesterone measured before the luteal phase
Labarta and Rodríguez (2020)	Best Practice & Research Clinical Obstetrics & Gynaecology	Progesterone use in assisted reproductive technology	Review paper
Lawrenz and Fatemi (2021)	Gynäkologische Endokrinologie	Gibt es optimale Serumprogesteronwerte in In-vitro-Fertilisations- und Kryozyklen? Can optimal serum levels of progesterone in in vitro fertilization and frozen embryo transfer cycles be defined?	Review paper
Niu et al. (2013)	Gynecological Endocrinology	Long-term pituitary downregulation before frozen embryo transfer could improve pregnancy outcomes in women with adenomyosis	No correlation between serum progesterone and outcomes
Patel et al. (2009)	Fertility and Sterility	Steady state levels of vaginally administered progesterone inserts (Endometrin) in frozen embryo transfer	No correlation between serum progesterone and outcomes

Pouget et al. (2020)	Human Reproduction (conference abstract)	Serum progesterone level on frozen embryo transfer day is lower with hormonal therapy than with a natural cycle, a retrospective single university centre study	No correlation between serum progesterone and outcomes
Setton et al. (2021)	Journal of Assisted Reproduction and Genetics	Detection of early placental hormone production in embryo transfer cycles lacking a corpus luteum	No correlation between serum progesterone and outcomes
Tarasconi et al. (2020)	Human Reproduction	Serum progesterone measurement and optimization reduce pregnancy loss in frozen-thawed embryo transfer cycles with hormone replacement therapy	Interventional study
Volovsky et al. (2020)	Journal of Assisted Reproduction and Genetics	Do serum progesterone levels on day of embryo transfer influence pregnancy outcomes in artificial frozen-thaw cycles?	Interventional study
Wambach et al. (2011)	Fertility and Sterility	Mode of Luteal Phase Progesterone Support After Frozen Embryo Transfer Does Not Affect Live Birth Rates	No correlation between serum progesterone and outcomes
Weiss et al. (2021)	European Journal of Obstetrics, Gynaecology and Reproductive Biology	Should the modified natural cycle protocol for frozen embryo transfer be modified? A prospective case series proof of concept study	No correlation between serum progesterone and outcomes
Zhang et al. (2015)	Chinese Journal of Integrated Medicine	Clinical observations of sequential therapy with Chinese medicine and hysteroscopic mechanical stimulation of the endometrium in infertile patients with repeated implantation failure undergoing frozen-thawed embryo transfer	No correlation between serum progesterone and outcomes
Álvarez et al. (2021)	Human Reproduction	Individualised luteal phase support in artificially prepared frozen embryo transfer cycles based on serum progesterone levels: a prospective cohort study	Interventional study

Supplemental Table 2. Correspondence with study authors.

Author, year	Journal	Title	Contacted	Response	Decision
Akaeda et al. (2019)	Clinical and Experimental Obstetrics & Gynecology	Relationship between serum progesterone concentrations and pregnancy rates in hormone replacement treatment-frozen embryo transfer using progesterone vaginal tablets	Yes	Pending	Included
Alsbjerg et al. (2018)	Reproductive BioMedicine Online	Progesterone levels on pregnancy test day after hormone replacement therapy-cryopreserved embryo transfer cycles and related reproductive outcomes	Yes	Pending	Included
Alsbjerg et al. (2020)	Reproductive BioMedicine Online	Can combining vaginal and rectal progesterone achieve the optimum progesterone range required for implantation in the HRT-FET model?	Yes	Pending	Included
Bar Hava et al. (2020)	Reproductive Biology	GnRHa for trigger and luteal phase support in natural cycle frozen embryo transfer – A proof of concept study	Yes	Pending	Awaiting classification
Basnayake et al. (2018)	Australian and New Zealand Journal of Obstetrics and Gynaecology	Progesterone concentrations and dosage with frozen embryo transfers - What's best?	Yes	Pending	Included
Bedient et al. (2020)	Fertility and Sterility (conference abstract)	Predictors of endometrial compaction prior to thawed blastocyst transfer	Yes	Pending	Awaiting classification
Boynukalin et al. (2019)	Reproductive Biology and Endocrinology	Measuring the serum progesterone level on the day of transfer can be an additional tool to maximize ongoing pregnancies in single euploid frozen blastocyst transfers	Yes	Yes	Included
Cédrin-Durnerin et al. (2019)	Reproductive BioMedicine Online	Serum progesterone concentration and live birth rate in frozen–thawed	Yes	Pending	Excluded

		embryo transfers with hormonally prepared endometrium			
Chang et al. (2019)	Fertility and Sterility	Increasing luteal progesterone levels are associated with higher ongoing pregnancy rates and lower early pregnancy losses following single euploid frozen embryo transfer	Yes	Pending	Awaiting classification
Commissaire et al. (2020)	Journal of Gynecology Obstetrics and Human Reproduction	Serum progesterone level and ongoing pregnancy rate following frozen-thawed embryo transfer after artificial endometrial preparation: a monocentric retrospective study	Yes	Yes	Included
Enatsu et al. (2018)	Reproductive Medicine and Biology	Effectiveness of high-dose transvaginal progesterone supplementation for women who are undergoing a frozen-thawed embryo transfer	Yes	Pending	Excluded
Gaggiotti-Marre et al. (2019)	Gynecological Endocrinology	Low serum progesterone the day prior to frozen embryo transfer of euploid embryos is associated with significant reduction in live birth rates	Yes	Pending	Included
Gaggiotti-Marre et al. (2020)	Human Reproduction	Low progesterone levels on the day before natural cycle frozen embryo transfer are negatively associated with live birth rates	Yes	Pending	Included
González-Foruria et al. (2020)	Reproductive BioMedicine Online	Factors associated with serum progesterone concentrations the day before cryopreserved embryo transfer in artificial cycles	Yes	Yes	Included
Ichiyama et al. (2018)	Journal of Obstetrics and Gynaecology Research	Does variable luteal support according to the serum progesterone level at the embryo transfer improve the clinical pregnancy rate of natural frozen-thawed embryo transfer?	No contact details found	NA	Awaiting classification

Kakkad et al. (2019)	Fertility and Sterility (conference abstract)	Serum progesterone level: a predictor of pregnancy in vitrified-warmed blastocyst transfer	No contact details found	NA	Included
Kawachiya et al. (2019)	Reproductive Medicine and Biology	Endogenous progesterone levels could predict reproductive outcome in frozen embryo replacement cycles supplemented with synthetic progestogens: A retrospective cohort study	Yes	Yes	Included
Kofinas et al. (2015)	Journal of Assisted Reproduction and Genetics	Serum progesterone levels greater than 20 ng/dl on day of embryo transfer are associated with lower live birth and higher pregnancy loss rates	Yes	Pending	Included
Kondapalli et al. (2015)	Fertility and Sterility (conference abstract)	Elevated serum progesterone reduces the likelihood of live birth after frozen transfer of euploid embryos: too much of a good thing?	Yes	Pending	Awaiting classification
Labarta et al. (2017)	Human Reproduction	Low serum progesterone on the day of embryo transfer is associated with a diminished ongoing pregnancy rate in oocyte donation cycles after artificial endometrial preparation: a prospective study	Yes	Yes	Included
Labarta et al. (2021)	Human Reproduction	Impact of low serum progesterone levels on the day of embryo transfer on pregnancy outcome: a prospective cohort study in artificial cycles with vaginal progesterone	Yes	Yes	Included
Lee et al. (2017)	Human Reproduction	A randomized double-blinded controlled trial of hCG as luteal phase support in natural cycle frozen embryo transfer	Yes	Pending	Awaiting classification
Liu et al. (2018)	Minerva Endocrinologica	The relationship between the hormone levels before	Yes	Pending	Awaiting classification

		transplantation and the outcomes of hormone replacement therapy frozen embryo transfer			
NCT04114500	ClinicalTrials.gov	The Association Between Serum E2 and P on the Day of FET and the Pregnancy Outcome (FET)	No contact details found	NA	Awaiting classification
Polat et al. (2020)	Reproductive BioMedicine Online	Addition of intramuscular progesterone to vaginal progesterone in hormone replacement therapy in vitrified-warmed blastocyst transfer cycles	Yes	Yes	Included
Pouget et al. (2020)	Human Reproduction (conference abstract)	Serum progesterone level on frozen embryo transfer day is lower with hormonal therapy than with a natural cycle, a retrospective single university centre study	Yes	Yes	Excluded
Ramos et al. (2020)	Gynecological Endocrinology	Is there a link between plasma progesterone 1–2 days before frozen embryo transfers (FET) and ART outcomes in frozen blastocyst transfers?	Yes	Yes	Included
Volovsky et al. (2020)	Journal of Assisted Reproduction and Genetics	Do serum progesterone levels on day of embryo transfer influence pregnancy outcomes in artificial frozen-thaw cycles?	Yes	Pending	Excluded
Whynott et al. (2021)	F&S Reports	The Effect of Weight and Body Mass Index (BMI) on Serum Progesterone Values and Live Birth Rate in Cryopreserved In Vitro Fertilization (IVF) Cycles	Yes	Pending	Awaiting classification
Xiao (2019)	Human Reproduction (conference abstract)	The correlation between serum progesterone level and clinical outcomes in hormone replacement	No contact details found	NA	Awaiting classification

		prepared thawed embryo transfer cycle			
Yovich et al. (2015)	Reproductive BioMedicine Online	Mid-luteal serum progesterone concentrations govern implantation rates for cryopreserved embryo transfers conducted under hormone replacement	Yes	Yes	Included
Zarei et al. (2018)	Journal of Evolution of Medical and Dental Sciences	Evaluation of correlation of serum progesterone level with pregnancy ocurrence in frozen embryo transfer	Yes	Pending	Awaiting classification

Supplemental Table 3. Quality of included studies according to the Newcastle-Ottawa Scale for the assessment of cohort studies.

	Selection				Comparability	Outcome			
Study	**Representativeness of exposed cohort**	**Selection of non-exposed cohort from same source as exposed cohort**	**Ascertainment of exposure**	**Outcome of interest not present at study start**	**Comparability of cohorts on the basis of the design or analysis**	**Outcome assessment**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow-up**	**Total score / maximum applicable to study**
Yovich et al. (2015)	*	*	*	*	**	*	*	*	9/9
Kofinas et al. (2015)	*	*	*	*	**	Unclear	*	*	8/9
Akaeda et al. (2019)	*	*	*	*	Unclear	Unclear	*	*	6/9
Labarta et al. (2017)	*	*	*	*	**	*	*	*	9/9
Basnayake et al. (2018)	*	*	*	*	**	Unclear	*	*	8/9
Alsbjerg et al. (2018)	*	*	*	*	**	Unclear	*	*	8/9
Kawachiya et al. (2019)	*	*	*	*	NS/unclear[1]	Unclear	*	*	6/9
Gaggiotti-Marre et al. (2019)	*	*	*	*	Unclear	Unclear	*	*	6/9
Kakkad et al. (2019)	*	*	*	*	**	Unclear	*	*	8/9
Boynukalin et al. (2019)	*	*	*	*	**	Unclear	*	*	8/9
Polat et al. (2020)	*	*	*	*	**	*	*	*	9/9
Alsbjerg et al. (2020)	*	*	*	*	**	Unclear	*	*	8/9
González-Foruria et al. (2020)	*	*	*	*	NA[2]	NS[4]	*	*	6/7
Commissaire et al. (2020)	*	*	*	*	**	NS[4]	*	*	8/9
Gaggiotti-Marre et al. (2020)	*	*	*	*	**	Unclear	*	*	8/9
Shiba et al. (2020)	*	*	*	*	**	Unclear	*	*	8/9
Ramos et al. (2020)	*	*	*	*	NS[3]	NS[4]	*	*	6/9

Liu and Wu (2020)	*	*	*	*	**	Unclear	*	*	8/9
Al Jarrah et al. (2021)	*	*	*	*	**	Unclear	*	*	8/9
Alyasin et al. (2021)	*	*	*	*	**	Unclear	*	*	8/9
Labarta et al. (2021)	*	*	*	*	**	*	*	*	9/9

Appendix 3: Protocol v1.2 for "Serum progesterone levels on the day of frozen embryo transfer and pregnancy outcomes: a prospective, multicentre cohort study" (Chapter 4)

STUDY PROTOCOL – SERUM PROGESTERONE LEVELS ON THE DAY OF FROZEN EMBRYO TRANSFER (FET) AND PREGNANCY OUTCOMES: A PROSPECTIVE, MULTICENTRE COHORT STUDY

Version Number: 1.2

Version Date: 8th December 2019

CARE FERTILITY, UK

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Protocol Amendments

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**
1	*11th August 2019*	*0.2*	*Substantial amendments based on feedback from IG and AT*	*Changes in study protocol* *Change in protocol template according to BCTU guidance*
2	*21st September 2019*	*0.3*	*Tracked changes accepted by PM*	*Tracked changes accepted by PM and sent to AC for review*
3	*3rd November 2019*	*1.0*	*Final version following IRB feedback*	*Sample size calculation included* *DMEC members updated* *CARE FET protocol detailed* *Subgroup analyses declared* *References updated* *Additional clarification of outcomes*
4	*27th November 2019*	*1.1*	*Additional amendments following Oonagh Pickering's and CARE Governance team's feedback*	*Changes to Protocol, ICF and PIS regarding informing GP*
5	*8th December 2019*	*1.2*	*Additional amendments following Malcolm Price's and Ioannis Gallos' feedback*	*Changes to Protocol with further statistics input*

Funding and Support in Kind

Funding and Support in Kind

Funder (s) (Names and contact details of all organisations providing funding and/or support in kind for this study)	Financial and non-financial support given:
CARE Fertility, UK	Funds for this project will be sourced from CARE Fertility's operational budget
CARE Fertility personnel will be involved in the collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication.	

Protocol Sign Off

CI Signature Page	
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol. I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of CARE Fertility. I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given. In addition, any discrepancies from the study as planned in this protocol will be explained. This protocol has been approved by the Chief Investigator and local Principal Investigators.	
Study Name:	To investigate the association between serum progesterone levels on the day of frozen embryo transfer (FET) and pregnancy outcomes
Protocol Version Number:	Version: 1.2
Protocol Version Date:	08/12/2019
CI Name:	Arri Coomarasamy
Trial Role:	Chief Investigator
Signature and date:	_____ __ __/__ __/__ __ __ __

PI Signature Page	
The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the study in compliance with the approved protocol. I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of CARE Fertility.	
Study Name:	To investigate the association between serum progesterone levels on the day of frozen embryo transfer (FET) and pregnancy outcomes
Protocol Version Number:	Version: 1.2
Protocol Version Date:	08/12/2019
PI Name:	
Name of Site:	
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PI Name:	
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Administrative Information

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Data Monitoring and Ethics Committee - DMEC
Chair: Dr Colin Howles, Honorary Fellow - University of Edinburgh Independent Member: Dr Adam Devall, Trials Management Team Leader – Birmingham Clinical Trials Unit Independent Member: Mrs Oonagh Pickering, Research Nurse - Tommy's National Centre for Miscarriage Research

Study Office Contact Details	
Dr Pedro Melo	ST5 in Obstetrics and Gynaecology PhD Candidate in Reproductive Medicine – Institute of Metabolism and Systems Research
Institute of Metabolism and Systems Research University of Birmingham Edgbaston, Birmingham B15 2TT	

Project Summary

Frozen embryo transfer (FET) cycles have become more common in recent years due to a push towards elective single embryo transfer (SET). While it is known that progesterone supplementation during the luteal phase improves clinical pregnancy rates, there is a paucity of prospective data on the impact of serum progesterone levels on pregnancy outcomes in FET cycles. This multicentre prospective cohort study will investigate the association between serum progesterone levels on the day of FET and pregnancy outcomes, and determine a serum progesterone cut-off value above which clinical pregnancy and live birth are more likely to occur. Women undergoing Assisted Reproductive Treatment with FET (ART-FET) at CARE Fertility clinics in the UK will be recruited and their serum progesterone measured on the day of frozen embryo transfer. Follow-up data will be stored in electronic patient records and analysed to determine whether a low serum progesterone level on the day of FET adversely affects ART outcomes.

Protocol title: Investigation of the association between serum progesterone levels on the day of frozen embryo transfer (FET) and pregnancy outcomes

Objectives: The aims of this study are the following:

- To investigate the association between serum progesterone levels on the day of FET and pregnancy outcomes
- To determine a serum progesterone cut-off value above which ongoing pregnancy and live birth are more likely to occur in FET cycles

Study Design

Study type: multicentre prospective cohort study conducted nationally at several CARE Fertility clinics in the UK

Patients: women undergoing ART with FET

Inclusion criteria: all women undergoing ART with FET

Exclusion criteria: none.

Participant Population

. Patient characteristics will include:

- Age
- Ethnicity
- Parity
- BMI
- Social history – smoking status, alcohol intake
- Timing of infertility (primary / secondary)
- Previous failed cycles / recurrent implantation failure / recurrent miscarriages
- Cause of infertility (e.g. anovulation, tubal factor, uterine factor, male factor, combined, unexplained)
- Ovarian reserve parameters (e.g. day 2-5 anti-müllerian hormone [AMH], follicle-stimulating hormone [FSH], estradiol and antral follicle count [AFC])
- Characteristics of ART cycle (e.g. IVF, ICSI)
- Duration of embryo cryopreservation
- Ultrasound features on the day of FET (e.g. endometrial thickness, AFC)

- Number and quality of embryos transferred (mean ± SD or median ± IQR)

Sample Size and Duration of the Study

We aim to enroll a total of 900 patients from participating CARE Fertility clinics over the course of 8 months.

Interventions

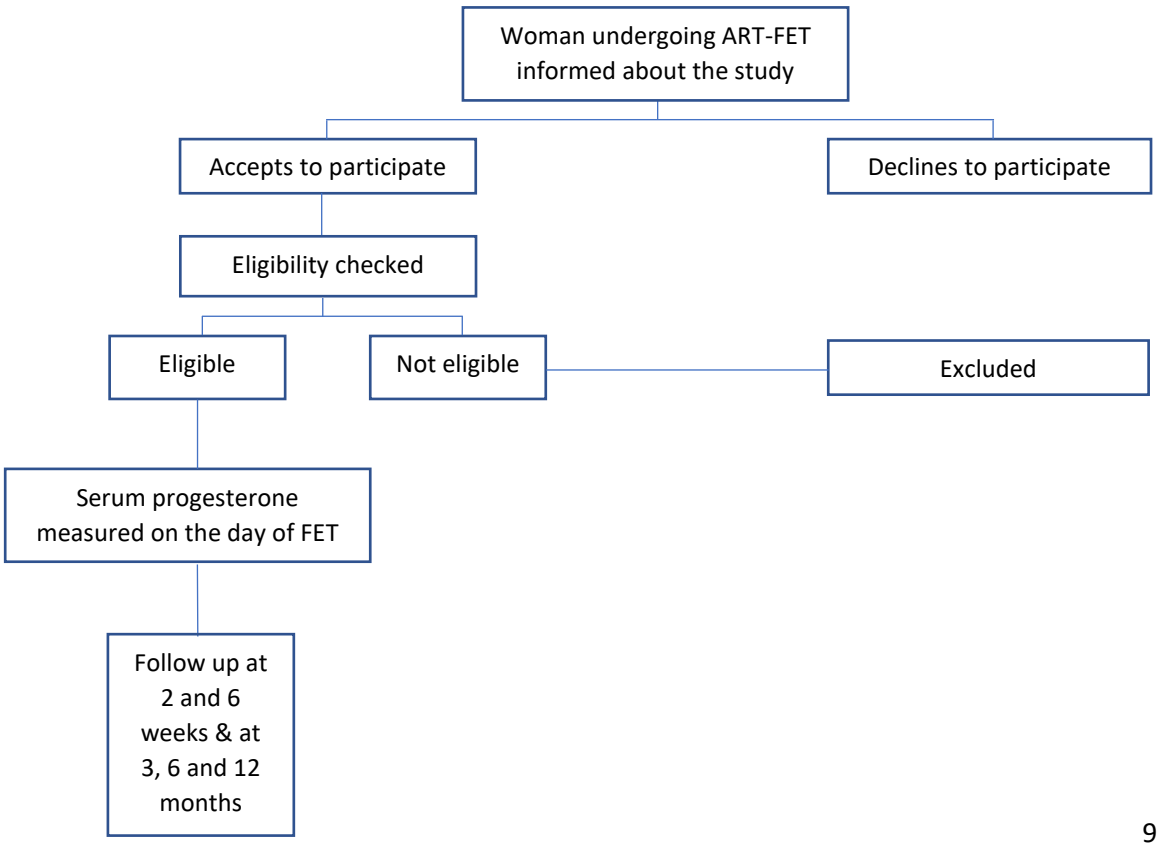
On the day of FET, venous blood will be obtained from consenting women and serum progesterone measurement will be taken. Patients and clinicians will be blinded to the test results for the entire duration of the study and follow-up.

Outcome Measures

Outcome data will be recorded in the CARE Fertility electronic patient database and collated for subsequent analyses. Outcomes to be assessed will include:

1. Live birth rate after 24 weeks of gestation per participant (n/n, %)
2. Miscarriage rates per participant (any clinical pregnancy lost before pregnancy week 12) (n/n, %)
3. Implantation rates per participant (number of gestational sacs seen in a 2D transvaginal ultrasound scan divided by the number of embryos transferred per patient) (n/n, %)
4. Biochemical pregnancy rates per participant (positive pregnancy test following embryo transfer) (n/n, %)
5. Clinical pregnancy rates per participant (presence of at least one gestational sac on ultrasound) (n/n, %)
6. Ectopic pregnancy rates per participant (n/n, %)

Trial Schema



1. Background and Rationale

Assisted reproductive technology (ART) procedures have evolved in recent decades to include complex ovarian stimulation protocols, *in vitro* treatment and cryopreservation of gametes and embryos, and adjuvant interventions aimed at improving outcomes (Chambers et al, 2009). In addition to female age, the main factors determining ART success include embryo quality and endometrial receptivity (Gallos et al, 2018).

Worldwide there has been a recent shift towards a single embryo transfer (SET) policy aimed at reducing complications linked to multiple pregnancy, and in 2017 the Human Fertilisation and Embryology Authority (HFEA) reported a fall in the multiple pregnancy rate in ART to 10% from 24% in 2008 (HFEA, 2019). Embryo cryopreservation has become increasingly common, not only as a consequence of the nearly universal push towards SET, but also because frozen embryo transfer (FET) cycles avoid maternal morbidity such as ovarian hyperstimulation syndrome (OHSS) (Mackens et al, 2017).

Despite the aforementioned developments, endometrial preparation protocols have evolved little since the inception of ART (Kawachiya et al, 2018). Hormonal replacement with oestrogen and progesterone during the luteal phase has been shown to increase endometrial thickness and induce an immune-tolerant environment in women undergoing treatment, thus favouring FET outcomes (Silverberg et al, 1991; Nawroth and Ludwig, 2005; Van der Linden et al, 2015). Nevertheless, to date there has been no consensus on the optimal endometrial preparation regimen to be used in FET in terms of safety and efficacy (Mackens et al, 2017).

Recent data have demonstrated an association between low serum progesterone and reduced ongoing pregnancy and live birth rates in FET cycles (Labarta et al, 2017; Gaggiotti-Marre et al, 2019). However, there have been no prospective national studies aimed at determining whether serum progesterone levels on the day of FET are predictive of pregnancy outcomes. We propose a large multicentre cohort study to determine a cut-off value of serum progesterone on the day of FET above which live birth is more likely to occur.

2. Aims and Objectives

The aims of this study are the following:

- To investigate the association between serum progesterone levels on the day of FET and pregnancy outcomes
- To determine a serum progesterone cut-off value above which ongoing pregnancy and live birth are more likely to occur in FET cycles

3. Study Design and Setting

3.1. Study design

This multicentre prospective cohort study will be conducted at several CARE Fertility clinics in the UK between November 2019 and June 2020. Ethical approval will be sought from a local institutional review board (IRB).

3.2. Study Population

Women undergoing ART-FET during the study period will be approached with details about the study and a patient information sheet (PIS) will be provided. Consenting women will be enrolled and their demographic details recorded to be used in analyses pertaining solely to this study. Patient characteristics will include:

- Age
- Ethnicity
- Parity
- BMI
- Social history – smoking status, alcohol intake
- Timing of infertility (primary / secondary)
- Previous failed cycles / recurrent implantation failure / recurrent miscarriages
- Cause of infertility (e.g. anovulation, tubal factor, uterine factor, male factor, combined, unexplained)
- Ovarian reserve parameters (e.g. day 2-5 anti-müllerian hormone [AMH], follicle-stimulating hormone [FSH], estradiol and antral follicle count [AFC])
- Characteristics of ART cycle (e.g. IVF, ICSI)
- Duration of embryo cryopreservation
- Ultrasound features on the day of FET (e.g. endometrial thickness, AFC)
- Number and quality of embryos transferred (mean ± SD or median ± IQR)

3.3. Sample size

We aim to enroll 900 patients from all participating CARE Fertility clinics over the course of 8 months.

A literature review performed by the study coordinators has indicated a 14% higher live birth rate (LBR) in women whose serum progesterone measurement was “high” (above 30-50 nmol/L) on or around the day of FET when compared to those whose progesterone level was “low” (Figure 1).

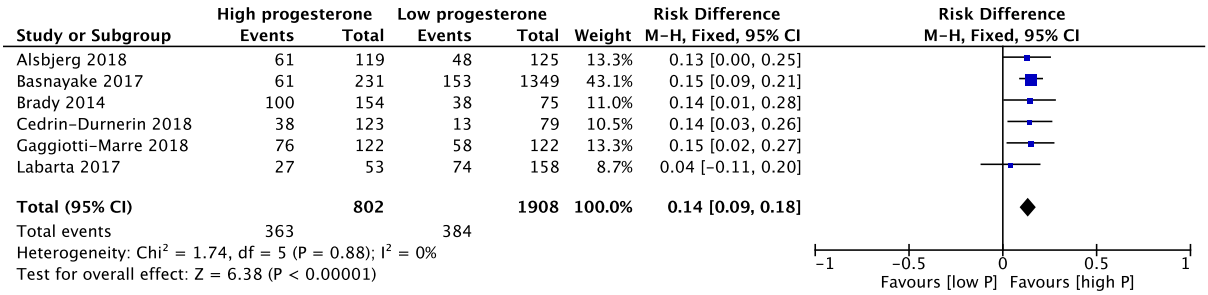


Figure 1. Meta-analysis of cohort studies evaluating the live birth rate in women with high vs. low serum progesterone around the time of FET. *FET,* frozen embryo transfer

The study by Brady et al, 2017 revealed the highest LBR among the reviewed manuscripts (65% vs. 51% in women with high vs. low progesterone respectively). In order to reach a power of 90% for a 14% difference between groups and an α value of 0.05, the total sample size required for our study would be 518 participants.

Taking into account factors such as attrition, heterogeneity and a potential overestimation of effect (i.e., a difference between groups lower than 14%), a conservative estimation of 900 participants has been agreed by consensus among the study coordinators. This will power the study to at least 85.6% in detecting a difference as low as 10% between groups, as shown in the following table:

Sample size	Alpha	LBR low progesterone	LBR high progesterone	Power
900	0.05	10%	20%	98.8%
			25%	100%
900	0.05	20%	30%	93.5%
			35%	99.9%
900	0.05	30%	40%	88.3%
			45%	99.7%
900	0.05	40%	50%	85.6%
			55%	99.5%
900	0.05	50%	60%	85.6%
			65%	99.6%
900	0.05	60%	70%	88.3%
			75%	99.8%

Currently approximately 2000 cycles are carried out annually at the CARE Fertility clinics that will participate in the study. Over the course of 8 months, approximately 1340 FET cycles are performed. Assuming a conservative uptake of 70% for this observational study, our final sample size would be 938 participants.

4. Eligibility

4.1. Inclusion criteria

All women undergoing ART with FET.

4.2. Exclusion criteria

None. We aim to study the "every day" patient undergoing FET, and for this we intend to keep the population of the study as unselected as possible.

5. Consent

Consent for participation in the study will be obtained by the recruiting clinician at the time of decision to undergo ART-FET. A Participant Information Sheet (PIS) will be provided to facilitate the process of consent. Investigators or their delegates will ensure that they adequately explain to the potential participant the aim of the study, anticipated benefits and possible hazards of taking part. They will also highlight that participation is voluntary and that the woman is free to decline to take part and may withdraw from the study at any time. The participant will be given the time between two appointments to read the PIS and to discuss their participation with others outside of the site research team. Additionally, the participant will be given the opportunity to ask questions before signing and dating the latest version of the Informed Consent Form.

The investigator or their delegate will then sign and date the ICF. A copy of the ICF will be given to the participant; a second copy will be filed in the woman's medical notes; and the original will be placed in the Investigator Site File (ISF).

6. Recruitment and Enrolment

Participants will be identified by the clinical team responsible for discussing and administering treatment with ART-FET. The patient's existing clinical care team will have access to patient records without explicit consent in order to identify potential participants, check whether they meet the inclusion criteria or make the initial approach to patients.

7. Study procedures

Details of all IVF cycles will be recorded. Endometrial preparation will follow routine medicated cycle FET protocols. Women undergoing FET cycles at CARE Fertility are treated according to the following protocol as per standard practice:

A. On day one of the menstrual cycle/withdrawal bleed, commence oestradiol valerate tablets (2mg three times daily, orally)
B. On day 10/11 of oestradiol valerate therapy, women undergo a transvaginal ultrasound scan. Where endometrial thickness is found to be ≥8mm, women are asked to commence progesterone pessaries (vaginal) at a dose of 400 mg twice daily, starting on days 12-15 of the cycle. This sometimes has to be delayed according to ultrasound findings (endometrial thickness) and local scheduling
C. Embryo replacement takes place approximately 122-126 hours following initiation of progesterone therapy, i.e. days 17-21 of the hormone replacement therapy cycle.

For the purpose of the proposed observational study, the only added step will be that on the day of FET, venous blood will be obtained from consenting women and serum progesterone measurement will be undertaken. Patients and clinicians will be blinded to the test results for the entire duration of the study and follow-up.

8. Outcome measures

8.1. Follow-up

Follow-up will be conducted as per routine CARE Fertility protocols to include a blood test for hCG where necessary, early pregnancy scan where there is a positive test or follow-up consultation where the outcome is negative or where there is early pregnancy loss. All women will be followed up until information on each outcome (and each possible adverse event) is collected.

8.2. Outcomes

Outcome data will be recorded in the CARE Fertility electronic patient database and collated for subsequent analyses. Outcomes to be assessed will include:

1. Live birth rate after 24 weeks of gestation per participant (n/n, %)
2. Miscarriage rates per participant (any clinical pregnancy lost before pregnancy week 12) (n/n, %)
3. Implantation rates per participant (number of gestational sacs seen in a 2D ultrasound divided by the number of embryos transferred per patient) (n/n, %)
4. Biochemical pregnancy rates per participant (positive serum hCG following embryo transfer) (n/n, %)

5. Clinical pregnancy rates per participant (presence of at least one gestational sac on ultrasound) (n/n, %)
6. Ectopic pregnancy rates per participant (n/n, %)

9. Adverse Event Reporting

Although adverse events from venipuncture are uncommon, any events requiring follow-up by the patient's general practitioner (GP) or the clinic personnel will be recorded in the participant's clinical notes. IVF protocols will be carried out in accordance with HFEA guidance and safety criteria. In view of the study's observational nature, no additional safety considerations will be required.

10. Data Handling and Record Keeping

10.1. Data Security

Data will be stored in the CARE Fertility electronic patient record system in accordance with the Data Protection Act 2018. Patients and clinicians will be blinded to the result of the serum progesterone measurement on the day of embryo transfer. Patient data will be anonymised for the purposes of statistical analysis.

11. Quality Control and Quality Assurance

This study will be conducted according to the principles of Good Clinical Practice.

12. Project Duration and End of Project Definition

Patient recruitment will occur over the course of 8 months. Data analysis, manuscript writing and publication will take place over the subsequent 12 months to account for patients who carry their pregnancies to term having enrolled at the end of the recruitment period.

13. Statistical Considerations

13.1. Sample Size

We aim to enroll 900 patients from all participating CARE Fertility clinics over the course of 8 months, as per the above calculation.

13.2. Analysis of Outcome Measures

Participants' progesterone levels will be analysed as a continuous variable and, if applicable, women will be assigned to one of 10 deciles according to their serum progesterone level to allow for categorical variable analyses. The Chi-square test (or Fisher's exact test where applicable) will be used to look for differences in categorical variables, while a Student's test (or an equivalent non-

parametric where the data are not normally distributed) will test differences between groups for continuous variables.

The association between progesterone and pregnancy outcomes will be assessed using logistic regression. Analysis 1 – progesterone only; analysis 2 – progesterone and demographic variables; analysis 3 – all of the variables. Both univariable and multivariable analyses will be used to adjust for potential confounding factors, including age, BMI, parity, ethnicity and smoking status.

For all continuous predictors, we will assess whether the effect on outcome is linear on the logit scale. If not, we will incorporate the variables using non-linear function.

To define the optimal progesterone threshold to predict clinical pregnancy and live birth, a receiving operating characteristic (ROC) curve will be identified and the area under the curve (AUC) calculated.

Where data are available, subgroup analyses will be carried out for women undergoing donor egg FET cycles, as well as in a cohort of women with optimal features for FET success (including age ≤ 35 years, BMI < 30 kg/m^2, endometrial thickness ≥7mm, single and euploid blastocyst transfer, no history of previous implantation failure or pregnancy loss, no history of uterine or tubal pathology). We will additionally carry out a subgroup analysis according to the route of progesterone administration (vaginal, rectal, subcutaneous and intramuscular, or any combination of administration routes).

14. Ethical Considerations

Ethics approval will be sought from the local IRB.

15. Confidentiality and Data Protection

Personal data recorded for the purposes of the study will be regarded as strictly confidential and handled and stored in accordance with the Data Protection Act 2018.

Participants will always be identified using their unique trial identification number.

16. Financial and Other Competing Interests

Funds for this project will be sourced from CARE Fertility's operational budget. The investigators declare no conflicts of interest that may significantly affect the trial.

17. Post-study care

The results of this study are likely to advance knowledge about the importance of adequate progesterone supplementation at the time of FET. Moreover, the study may ultimately inform future randomised controlled trials on additional progesterone supplementation in women with low serum progesterone levels to assess whether this improves pregnancy outcomes in FET cycles.

18. Publication Policy

Dissemination of this study's results will be undertaken via scientific and social media, and locally to women undergoing ART-FET cycles in CARE Fertility clinics. The investigators will seek publication of the study's results in a peer-reviewed journal within the field of ART. The manuscript will be prepared by Dr Pedro Melo and authorship will be determined according to the individual's degree of contribution to the study and writing of the manuscript.

19. Reference List

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Gallos ID, Khairy M, Chu J, Rajkhowa M, Tobias A, Campbell A, Dowell K, Fishel S, Coomarasamy A. Optimal endometrial thickness to maximize live births and minimize pregnancy losses: analysis of 25,767 fresh embryo transfers. *Reprod Biomed Online* 2018;37(5):542-8. doi: 10.1016/j.rbmo.2018.08.025

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Labarta E, Mariani G, Holtmann N, Celada P, Remohi J, Bosch E. Low serum progesterone on the day of embryo transfer is associated with a diminished ongoing pregnancy rate in oocyte donation cycles after artificial endometrial preparation: a prospective study. *Hum Reprod* 2017;31(12):1-6

Mackens S, Santos-Ribeiro S, van de Vijver A, Racca A, Van Landuyt L, Tournaye H, Blockeel C. Frozen embryo transfer: a review on the optimal endometrial preparation and timing. *Hum Reprod* 2017;32(11):2234-42

Nawroth F, Ludwig M. What is the 'ideal' duration of progesterone supplementation before the transfer of cryopreserved-thawed embryos in estrogen/progesterone replacement protocols? *Hum Reprod* 2005;20(5):1127-34

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Appendix 4: Patient information sheet v1.2 for "Serum progesterone levels on the day of frozen embryo transfer and pregnancy outcomes: a prospective, multicentre cohort study" (Chapter 4)

ProFET - a study investigating the association between blood progesterone levels on the day of frozen embryo transfer (FET) and pregnancy outcomes

We would like to invite you to participate in a study to investigate whether there is a link between blood levels of progesterone on the day of frozen embryo transfer (FET) and a successful reproductive outcome. This research study will involve us gathering follow-up information about you and your care. Joining the study is entirely up to you. Before you choose to take part, it is important for you to understand why this study is being conducted and what it means for you. Please take time to read this Participant Information Sheet (PIS) carefully and decide whether you would like to participate.

What is the purpose of the study?

Although several clinical studies have demonstrated a clear link between low progesterone levels and pregnancy failure in IVF cycles, there has been little research into how a woman's progesterone levels relate to the success of a pregnancy following FET in particular. CARE Fertility are conducting a multicentre study across the UK that aims to identify whether there is an optimal range of progesterone levels in women's blood on the day of FET resulting in higher pregnancy success.

Why have I been chosen?

You were chosen because you are undergoing IVF with a frozen-thawed embryo and therefore fulfil the inclusion criteria of our study.

What would taking part involve?

If you agree to participate, on the day of your embryo transfer a nurse will collect a blood sample from you and your progesterone level will be measured in the laboratory. Neither you nor any of the staff involved in your care will know the result of the test in order to avoid the risk of inadvertently affecting the results of the study or your care. You will receive no additional medications apart from those previously agreed between you and your doctor as part of your IVF treatment. Taking part in this study will not require any additional follow-up apart from the routine clinical appointments you will receive as part of your IVF treatment. If you agree, we will keep you informed about the results of the study by sending you a newsletter containing our findings and how they are likely to affect future practice in women undergoing FET cycles.

What are the possible benefits of taking part?

By taking part in this study, you will be helping us to obtain more information about progesterone levels at the time of frozen embryo transfer. This may influence the way we treat women who undergo FET cycles in the future.

What are the possible disadvantages and risks of taking part?

The risks from taking part in this study are small. Most women do not experience any complications from having their blood taken apart from mild pain and occasional bruising.

Who is organising and funding the research?

This study is being organised and funded by CARE Fertility, UK.

What personal information about me will be recorded?

In addition to your serum progesterone level result, we would like your permission to use the information we have collected as part of your treatment (including details such as your age, weight, height, and the type of IVF you have received) for the purposes of anonymised data analysis. This does not require any additional information apart from the details you have already given us as part of your treatment.

Will my taking part in this study be kept confidential?

We will not use any information that could be used to identify you. All the information we collect during the course of the research will be kept confidential and there are strict laws that protect the privacy of the patient at every stage. All members of the research team are under a duty to keep your records private and confidential according to the Data Protection Act 1998.

Other researchers may wish to access data from this study in the future. However, it will not be possible to identify participants because available data will not include names, addresses or dates of birth. The study investigators will ensure that any other researchers comply with data protection and ethics guidelines. We will not inform your GP of your participation in this study without your explicit consent.

If requested by the Regulatory Authorities whose role it is to ensure that this research is properly conducted and that the interests of all participants are protected, it is a requirement that your records in this study, together with any relevant medical records, be made available to them. All of these individuals are under a duty to keep your records confidential.

What will happen to the samples I give?

The blood sample we obtain from you will be stored in a confidential manner for the duration of the study. We do not intend to share your samples with individuals that are not directly involved in conducting the study.

What if something goes wrong?

If you develop a concern about any aspect of this study, please ask to speak to a member of the research team and they will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this submitting a complaint to CARE via www.carefertility.com/contact-us or to the Human Fertilisation and Embryology Authority (HFEA) via their website on www.hfea.gov.uk/contact-us.

What if I do not want to take part?

If you withdraw from the study, we will destroy all your identifiable samples, but we may need to use the data collected up to your withdrawal in an anonymised manner. If you decide not to carry on, this will not affect your care.

What happens when the research study stops?

If you wish to be informed about the results of the study and how it may impact future fertility treatments, please provide your consent in the consent form that will be provided to you with this Information Sheet and we will be in touch.

Do you have any further questions?

If you would like to speak to someone about the study please contact:

Dr Pedro Melo, ProFET Study Coordinator

Email [redacted]

Appendix 5: Informed consent form for "Serum progesterone levels on the day of frozen embryo transfer and pregnancy outcomes: a prospective, multicentre cohort study" (Chapter 4)

Informed Consent – ProFET study

Study Title: Serum progesterone levels on the day of frozen embryo transfer and pregnancy outcomes

Centre ID/Site name: ___ ___ / _____ CARE Patient Number _____

Patient Initials:

Principal Investigator:

Please initial inside each box

1	I confirm that I have read and understood the information sheet, dated 08/12/2019 version number 1.2 for the ProFET study. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that data collected up to my time of withdrawal may be used as part of describing the study's timeline without directly identifying me.	☐
3	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the ProFET research team, the CARE Fertility clinical team responsible for my care and by regulatory authorities, where this is relevant to my taking part in this research. I give permission for these individuals to have direct access to my records.	☐
4	Data collected that identify me by name (e.g. consent forms) will be collected and stored in my CARE Fertility medical record. I understand that any identifiable data will be anonymised for the purposes of data analysis and publication of the study's results. I agree to the storage of these data.	☐
5	I agree to take part in the ProFET study. I understand that taking part in the study will not benefit the outcome of the IVF cycle I am currently undergoing. I agree to having my blood taken for the purpose of testing progesterone levels.	☐
6	I wish / do not wish (cross out option that does not apply) to receive information about the results of the study and how it may impact future fertility treatment.	☐
7	**(For partner):** I agree for my personal information to be accessed by the ProFET research team for data analysis purposes.	☐

_____	_____	_____
Name of Patient	*Date*	*Signature*
_____	_____	_____
Name of Partner	*Date*	*Signature*
_____	_____	_____
Name of Person taking Consent	*Date*	*Signature*

When completed: 1 for participant, 1 for Investigator Site File, 1 (original) to keep in medical notes.

Appendix 6: Confirmation of sponsorship from CARE Fertility for "Serum progesterone levels on the day of frozen embryo transfer and pregnancy outcomes: a prospective, multicentre cohort study" (Chapter 4)

Professor Arri Coomarasamy
Institute of Metabolism and Systems Research
University of Birmingham

Monday, 18 November 2019

Dear Professor Coomarasamy

Project Title: Serum Progesterone levels on the day of frozen embryo transfer (FET): a prospective, multicentre cohort study (The ProFET study)

Under the requirements of UK Policy Framework for Health and Social Care Research, CARE Fertility agrees to act as Sponsor for this project.

Sponsorship is subject to you obtaining a favourable ethical opinion and a 'capacity to deliver' opinion by the Clinical Research Group (CRG).

Failure to forward copies of approvals or required annual progress reports will result in withdrawal of Sponsorship and closure or transfer of the study as appropriate.

As Chief Investigator, you must ensure that local study recruitment does not commence until all applicable approvals have been obtained.

Following receipt of all relevant approvals, you should ensure that any subsequent amendments are notified to the Sponsor, the CARE Clinical Research Group and relevant Regulatory bodies.

You may show this letter to external organisations.

Yours sincerely,

Mr David Burford
Chief Executive Officer

Appendix 7: Capacity to deliver for "Serum progesterone levels on the day of frozen embryo transfer and pregnancy outcomes: a prospective, multicentre cohort study" (Chapter 4)

Professor Arri Coomarasamy
Institute of Metabolism and Systems Research
University of Birmingham

Monday, 18 November 2019

Dear Professor Coomarasamy

Project Title: Serum Progesterone levels on the day of frozen embryo transfer (FET): a prospective, multicentre cohort study (The ProFET study)

The CARE Clinical Research Group, consisting of representatives of the medical, nursing, embryology, administrative and governance team examined the PROTOCOL, INFORMATION SHEET, CONSENT FORM and ETHICS OPINION letter, and deemed that the CARE Fertility Clinics have the **Capacity to Deliver** the ProFET study without causing any significant changes to the care of patients. We therefore approve the conduct of the study in the CARE clinics.

Please ensure that you report any amendments to the study to the Clinical Research Group, in addition to any of the relevant authorities.

Yours sincerely

Professor Simon Fishel
Vice Chair of the CARE Clinical Studies Group

Appendix 8: Ethics approval for "Serum progesterone levels on the day of frozen embryo transfer and pregnancy outcomes: a prospective, multicentre cohort study" (Chapter 4)

12th December 2019

Dear Dr Melo,

Re: IRB Committee ethical approval

- **Full Title:** Serum Progesterone levels on the day of frozen embryo transfer and pregnancy outcomes: a prospective, multicentre cohort study
- **Sponsor/Applicant Institution:** CARE Fertility

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the protocol and supporting documentation as revised.

Approved trial documentation

Document name	Version number	Date
Protocol	1.2	08-Dec-2019
Informed Consent Form	1.2	08-Dec-2019
Patient Information Sheet	1.2	08-Dec-2019

IRB Committee composition

Name	Job title	IRB Committee role
Colin Howles	Honorary Fellow, University of Edinburgh	Chair
Adam Devall	Senior Clinical Trials Fellow, University of Birmingham	Committee member
Oonagh Pickering	Research Nurse for Tommy's Birmingham	Committee member

Yours faithfully,

[redacted]

Dr Colin Howles
Honorary Fellow, University of Edinburgh

Chair, CARE Fertility IRB Committee

Appendix 9: Confirmation of registration with Clinicaltrials.gov for "Serum progesterone levels on the day of frozen embryo transfer and pregnancy outcomes: a prospective, multicentre cohort study" (Chapter 4)

ID: ProFETStudy Serum Progesterone Levels on the Day of Frozen Embryo Transfer (FET) and Pregnancy Outcomes NCT04170517

Protocol Registration and Results System

Protocol Registration Preview

This is a rough approximation of how the Protocol Registration will appear on the ClinicalTrials.gov public web site.

Serum Progesterone Levels on the Day of Frozen Embryo Transfer (FET) and Pregnancy Outcomes (ProFET)

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04170517

Recruitment Status: Completed
First Posted: *
Last Update Posted: *

* Date not available in PRS

Sponsor:

CARE Fertility UK

Information provided by (Responsible Party):

CARE Fertility UK

Study Description

Brief Summary:

supplementation during the luteal phase improves clinical pregnancy rates, there is a paucity of prospective data on the impact of serum progesterone levels on pregnancy outcomes in FET cycles. This multicentre prospective cohort study aims to investigate the association between serum progesterone levels on the day of FET and pregnancy outcomes, and to determine a serum progesterone cut-off value above which clinical pregnancy and live birth are more likely to occur. Women undergoing ART-FET cycles at CARE Fertility clinics in the UK will be recruited and their serum progesterone measured on the day of frozen embryo transfer. Follow-up data will be stored in electronic patient records and analysed to determine whether a low serum progesterone level on the day of FET adversely affects ART outcomes.

Condition or disease	Intervention/treatment
Infertility Infertility, Female IVF	Diagnostic Test: Measurement of serum progesterone on the day of FET

Study Design

Study Type:	Observational
Actual Enrollment:	402 participants
Observational Model:	Cohort
Time Perspective:	Prospective
Official Title:	Serum Progesterone Levels on the Day of Frozen Embryo Transfer (FET) and Pregnancy Outcomes
Actual Study Start Date:	January 2, 2020
Actual Primary Completion Date:	February 28, 2021
Actual Study Completion Date:	December 31, 2021

Groups/Cohorts

Number of groups: 1

Intervention Details:

Diagnostic Test: Measurement of serum progesterone on the day of FET

Measurement of serum progesterone on the day of FET

Outcome Measures

Primary Outcome Measure:

1. Live birth rate per participant [Time Frame: 18 months]

Birth of a live fetus at 24 or more weeks of gestational age

1. Miscarriage rate per participant [Time Frame: 18 months]

   Any clinical pregnancy lost before week 12 of gestation per participant (number of events/number of participants, %)

2. Implantation rates per participant [Time Frame: 18 months]

   Number of gestational sacs seen in a 2D transvaginal ultrasound scan divided by the number of embryos transferred per patient (number of events/number of embryos transferred, %)

3. Biochemical pregnancy rate per participant [Time Frame: 18 months]

   Positive pregnancy test following embryo transfer per participant (number of events/number of participants, %)

4. Clinical pregnancy rate per participant [Time Frame: 18 months]

   Presence of at least one gestational sac on ultrasound (number of events/number of participants, %)

5. Ectopic pregnancy rate per participant [Time Frame: 18 months]

   number of events/number of participants, %

Eligibility Criteria

Ages Eligible for Study:	
Sexes Eligible for Study:	Female
Gender Based:	No
Accepts Healthy Volunteers:	Yes
Sampling Method:	Non-Probability Sample

Study Population

All women undergoing ART with FET.

Criteria

Inclusion Criteria:

- All women undergoing ART with FET.

Exclusion Criteria:

- None. We aim to study the "every day" patient undergoing FET, and for this we intend to keep the population of the study as unselected as possible.

ID: ProFETStudy Serum Progesterone Levels on the Day of Frozen Embryo Transfer (FET) and Pregnancy Outcomes NCT04170517

Contacts and Locations

Locations

United Kingdom

CARE Fertility Birmingham

Birmingham, United Kingdom

Investigators

Principal Investigator:	Arri Coomarasamy, MBChB MD FRCOG	CARE Fertility UK

More Information

Responsible Party:	CARE Fertility UK
ClinicalTrials.gov Identifier:	NCT04170517
Other Study ID Numbers:	ProFETStudy
Last Verified:	August 2022

Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD:	No
Plan Description:	No IPD will be shared with other researchers. Any IPD will be confined to the purposes of the study.

Human Subjects Protection Review Board Status: Approved

Studies a U.S. FDA-regulated Drug Product: No

Studies a U.S. FDA-regulated Device Product: No

U.S. National Library of Medicine | U.S. National Institutes of Heal h | U.S. Department of Health & Human Services | HHS Vulnerability Disclosure

Appendix 10: Protocol registration record (PROSPERO) for "Immunological therapies in women with subfertility" (Chapter 5)

Systematic review

A list of fields that can be edited in an update can be found here

1. * Review title.

Give the title of the review in English

Immunological therapies in women with subfertility

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

15/11/2021

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

15/01/2022

5. * Stage of review at time of this submission.

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Pedro Melo

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Melo

7. * Named contact email.

Give the electronic email address of the named contact.

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

Tommy’s National Centre for Miscarriage Research, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, B15 2TT, United Kingdom

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Birmingham

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr Pedro Melo. Tommy's National Centre for Miscarriage Research
Dr Teresa Thornton.
Professor Arri Coomarasamy. Tommy's National Centre for Miscarriage Research
Professor Ingrid Granne. University of Oxford

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

None

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Are immunological therapies efficacious and safe in women with subfertility and/or undergoing assisted conception? We aim to systematically identify, summarise and analyse interventional data from peer-review full-text studies investigating the effectiveness and safety of immunological therapies administered to women with subfertility and/or undergoing assisted conception (including for unexplained of male-factor subfertility).

P – Therapies with a modulatory effect on the immune system

C – Any other immune therapy, placebo or no intervention

O – Primary: ongoing pregnancy or live birth; miscarriage. Secondary: clinical pregnancy; adverse drug events; infection rate post-egg retrieval; oocyte number; embryo number; implantation rate.

S – Fertility clinic

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

We will perform extensive bibliographic searches according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Our searches will include the following databases:

1. MEDLINE (Ovid platform)
2. EMBASE (Ovid platform)
3. Cochrane Central Register of controlled trials

We will not apply any language restrictions to our searches.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

It is known that the ability to create a competent embryo depends on factors which are intrinsic to both the oocyte and sperm, as well as the interaction between the two gametes. Further, successful implantation relies on an effective dialogue between the maternal and embryonic interfaces. This entails the creation of a tolerant immune-endocrine milieu within the endometrium to allow for implantation of the semi-allogenic embryo. The knowledge that endometrial tolerance is essential for pregnancy success has led researchers to postulate that a heightened localised or systemic immune response may result in an inhospitable endometrium and implantation failure. Some authors also defend that even when successful attachment of the embryo occurs, women with an increased inflammatory response may be at a higher risk of pregnancy loss.

Apologists of immune therapies base their use on the notion that a subdued immune response may result in better outcomes for women trying to conceive. Immunomodulatory treatments commonly employed by fertility practitioners include corticosteroids, intralipid, intravenous immunoglobulin, tumour necrosis factor alpha inhibitors, anticoagulant drugs (aspirin, heparin), leukaemia inhibitory factor, granulocyte-colony stimulating factor and lymphocyte immune therapy. Yet there is no consensus on the efficacy and safety of these drugs in women trying to conceive.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

We will include women with subfertility trying to conceive naturally or with assisted reproductive technology.

We will exclude:

- Women with recurrent pregnancy loss, as defined by individual studies' investigators;

- Studies in which the intervention has been undertaken in vitro (for example, addition of granulocyte-colony stimulating factor to embryo culture media).

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

This systematic review will investigate the use of immunomodulatory drugs alone or in combination to

improve reproductive outcomes in women trying to conceive.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

The intervention will be compared to any other immunomodulatory therapy, or to placebo/no intervention.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

We will include full-text, peer reviewed studies where two or more groups (intervention 1 vs intervention2/control/placebo) have been compared to one another;

- Randomised controlled trials.

We will exclude the following studies:

- Non-peer reviewed studies;

- Conference abstracts;

- Case reports;

- Systematic reviews;

- Narrative reviews.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

1. Effectiveness: pregnancy or live birth.

2. Safety: miscarriage.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

We will express effect size as relative risk with 95% confidence intervals for categorical variables, and mean difference or standardised mean difference with 95% confidence interval for continuous variables.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate

to the review

The clinical pregnancy,

1. Clinical pregnancy;

2. Adverse drug events;

3. Infection rates post-transvaginal oocyte retrieval;

4. Oocyte number;

5. Embryo number;

6. Implantation rate.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

We will express effect size as relative risk with 95% confidence intervals for categorical variables, and mean difference or standardised mean difference with 95% confidence interval for continuous variables.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

We will include all full-text, peer-reviewed interventional studies investigating the effectiveness and safety of immunomodulatory therapies upon reproductive outcomes in women with subfertility.

The studies will be reviewed and selected by two independent reviewers (PM and TT), initially by assessing the title of the study and then reviewing the abstracts. Those studies deemed likely to meet the eligibility criteria will be subjected to full-text screening. Discrepancies between reviewers' assessments will be resolved by discussion and, where required, resolution will be sought with a third reviewer (AC or IG).

The main data to be collected will be:

- Authors and year of publication
- Country of origin
- Study design
- Population (inclusion and exclusion criteria) and number of participants
- Type of conception (natural or assisted)
- Data relating to primary and secondary outcomes as listed above

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

All randomised controlled trials deemed to meet the eligibility criteria will be assessed for quality and risk of bias using the Cochrane risk-of-bias (RoB 1) tool.

All cohort and case-control studies will be assessed for quality and risk of bias using the Newcastle-Ottawa

scale.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

We will include all cohort and case-control studies in a narrative synthesis for each intervention individually or used in combination. This will be supported by a “Characteristics of included studies” table.

Where sufficient studies are available, we will also conduct meta-analyses of randomised controlled trials for each intervention used alone or in combination. This will depend upon whether the clinical heterogeneity between studies is deemed acceptable. We will employ a random-effects model for meta-analysis, and use the I^2 statistic to assess statistical heterogeneity. We will consider $I^2$50% as indicative of low heterogeneity.

The meta-analyses will be carried out using Review Manager 5.4.1. (Cochrane Collaboration) and Stata Statistical Software version 17 (Texas, USA).

We will perform sensitivity analyses for the primary outcome measures according to the following criteria:

- Removing all studies deemed to be at unclear or high risk of bias (i.e. including solely studies at low risk of bias);
- Using a fixed-effects model for meta-analysis;
- Presenting results as odds ratio rather than relative risk.

29. * Analysis of subgroups or subsets.

State any planned investigation of ‘subgroups’. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

Where sufficient studies are identified, we will consider subgroup analyses according to patient profile (for example, type of infertility; age; body mass index; recurrent implantation failure; comorbidities known to result in heightened immune response/auto-immunity).

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
Yes

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly

No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
Yes

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

England

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or

The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

We plan to publish the systematic review in a peer-reviewed journal upon completion.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Infertility; immunomodulatory drugs; implantation failure; live birth; miscarriage.

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

Appendix 11: Methods description for "Immunological therapies in women with subfertility" (Chapter 5)

Methods (Chapter 5)

Registration

We registered this systematic review with PROSPERO (ID number CRD42021294031).

Search strategy

We conducted bibliographic searches according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The following electronic databases were systematically searched from inception until November 15, 2021: EMBASE (OVID platform), MEDLINE (OVID platform) and the Cochrane Central Register of Controlled Trials. Supplemental file 1 contains a detailed description of our search strategies for each platform. We additionally reviewed the reference lists of included publications to avoid missing other relevant studies. No language restrictions were applied to our searches.

Study selection

We selected studies for inclusion in a two-stage process using Covidence. Two review authors (P.M. and T.T.) independently screened the titles and abstracts of the references identified by the searches, followed by independent full-text screening and data extraction. Any discrepancies were resolved by consensus and, where needed, arbitration by a senior author (I.G. or A.C.).

We included peer-reviewed controlled interventional studies investigating the effect of immunological therapies upon the reproductive outcomes of women with subfertility and/or undergoing ART. The following interventions were included: aspirin, heparin, corticosteroids, granulocyte-colony stimulating factor, intralipid, intravenous immunoglobulin, tumour

necrosis factor-α inhibitors and leukaemia inhibitory factor, evaluated either alone or in combination, versus no intervention, placebo or any other immunomodulatory drug.

We excluded conference abstracts, studies where outcome data were reported per ovarian stimulation cycle or embryo transfer, manuscripts where women acted as their own controls during different treatment cycles, and studies assessing women with recurrent pregnancy loss (RPL). We also excluded studies where a pairwise comparison was made exclusively between different doses or routes of administration of the same drug. In studies comparing different doses of a drug to a control group (i.e., no intervention, or a different drug), we amalgamated outcome data from the arms in which different doses of the same drug were used.

Quality assessment

The quality of non-randomised interventional studies was independently assessed by two reviewers (P.M and T.T.) using the Newcastle-Ottawa scale (NOS), as recommended by the Cochrane Collaboration. These two authors also assessed the risk of bias of included randomized controlled trials (RCTs) using the Cochrane "Risk of bias" tool, which evaluates the following parameters: selection (random sequence generation and allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome assessors); attrition (incomplete outcome data); and reporting. We additionally assessed the risk of other bias and considered it to be high where trials conducted post-2010 were not registered prospectively or within six months of commencing recruitment; and where single-centre trials reported implausibly high recruitment rates.

Study outcomes

The primary effectiveness outcome of this review was the composite rate of ongoing pregnancy or live birth per participant (OPR or LBR). Ongoing pregnancy was defined as a viable intrauterine pregnancy at ≥12 weeks of gestation identified on ultrasound, and live birth was defined as the delivery of a live fetus after 22 weeks of pregnancy (17).

Data extraction process

Two reviewers (P.M. and T.T.) independently extracted study characteristics from the eligible articles, including country of origin, setting (single or multicentre), study design, duration, participants (inclusion and exclusion criteria), total number of participants analysed, intervention and control drug regimens, and outcome data of interest. We resolved disagreements by consensus.

Data synthesis and analysis

We classified participating women into the following subgroups: previous implantation failure, defined as one or more previous embryo transfers resulting in a negative pregnancy test; autoimmunity, defined as the presence of a known autoimmune condition (e.g., systemic lupus erythematosus) or positive autoimmune antibody testing (e.g. thyroid auto-immunity, positive antiphospholipid antibodies); high inflammation (e.g., high natural killer-cell activity elevation); thin endometrium according to the trialists' definition; low ovarian reserve or response, as defined by the trialists; good prognosis (e.g., unexplained infertility); and unselected, when the eligibility criteria were not specified by the study authors.

We performed all data analyses using Review Manager 5.4.1 (Cochrane, 2020). Effect sizes were described using risk ratio (RR) and respective 95% confidence interval (CI). We calculated effect estimates for all pairwise comparisons identified in the included studies. We elected to meta-analyse exclusively data from RCTs, to minimize the risk of bias associated with meta-analysis of cohort studies. In the RCT meta-analyses, we assessed the I^2 parameter to measure statistical heterogeneity, and considered I^2>50% as representative of high statistical heterogeneity, in line with the recommendations from Cochrane. All meta-analyses were conducted using a random effects model.

Subgroup analyses

The primary quantitative analysis included all RCTs investigating each pairwise comparison, irrespective of the participant characteristics. In addition, we conducted subgroup meta-analyses according to the aforementioned patient characteristic subgroups. The subgroup analyses aimed to determine whether the effectiveness of the intervention varied in relation to patient phenotype.

Evidence certainty

We created GRADE summary of findings (SOF) tables for the quantitative analyses (RCT data) using GRADEPro software. We assessed the certainty of the evidence for each of the following criteria: risk of bias; consistency; indirectness; imprecision; and publication bias. For each comparison, we documented our decisions in the assessment of these domains and judged the overall certainty of the evidence for each outcome as high-, moderate-, low- and very low-certainty.

Supplemental file 1 – description of searches

OVID platform (EMBASE and MEDLINE):

1. exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ or female infertility/
2. vitro fertili?ation.tw.
3. icsi.tw.
4. intracytoplasmic sperm injection$.tw.
5. ivf.tw.
6. assisted reproduct$.tw.
7. ovulation induc$.tw.
8. (ovari$ adj2 stimula$).tw.
9. COH.tw.
10. superovulat$.tw.
11. ovarian hyperstimulation.tw.
12. infertil$.tw.
13. subfertil$.tw.
14. (ovari$ adj2 induction).tw.
15. implantation failure$.tw.
16. (recurrent adj3 miscarriage$).tw.
17. (recurrent adj3 abortion$).tw.
18. (recurrent adj3 implantation$).tw.
19. recurrent pregnancy loss.tw.
20. or/1-19
21. exp heparin/
22. heparin$.tw.
23. LMWH$.tw.
24. liquemin.tw.
25. enoxaparin.tw.
26. heparinic acid.tw.
27. dalteparin.tw.
28. tinzaparin.tw.
29. clexane.tw.
30. lovenox.tw.
31. indenox.tw.
32. xaparin.tw.
33. acetylsalicylic acid/
34. (acetylsalicylic acid or aspirin).tw.
35. acetyl salicylic acid.tw.
36. exp granulocyte macrophage colony stimulating factor/
37. GM CSF.tw.
38. (EmbroGen or blastGen or blastogen or Leucomax).tw.
39. intralipid.tw.
40. ivig.tw.
41. intravenous immune globulin.tw.
42. intravenous immunoglobulin.tw.

43. lymphocyte immune therapy.tw.
44. leu#ocyte inhibitory factor.tw.
45. lit.tw.
46. lif.tw.
47. glucocorticoid$.tw.
48. methylprednisolone$.tw.
49. prednisolone$.tw.
50. steroid$.tw.
51. corticosteroid$.tw.
52. tnf inhibit$.tw.
53. exp tumour necrosis factor inhibitor/
54. (etanercept or adalimumab or infliximab or certolizumab or golimumab).tw.
55. peripheral blood mononuclear cells.tw
56. pbmc.tw
57. or/21-56
58. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
59. 57 not 58
60. 20 and 57 and 59
61. limit 60 to human
62. remove duplicates from 61

CENTRAL search strategy:

"infertil" or "subfertil" or "in vitro fertil" or "ivf" or "superov" or "ovarian stimulation" or "ovarian hyperstimulation" or "COH" or "assisted reprod" or "assisted concep" or "assisted reprod" or "ICSI" or "IVF" or "implantation fail"

AND

"acetylsalicylic acid" or "aspirin" or "heparin" or "LMWH" or "liquemin" or "enoxaparin" or "heparinic acid" or "dalteparin" or "tinzaparin" or "clexane" or "lovenox" or "indenox" or "xaparin" or "steroid" or "glucocorticoid" or "methylprednisolone" or "prednisolone" or "intralipid" or "intravenous immunoglobulin" or "IVIG" or "granulocyte-colony stimulating factor" or "granulocyte macrophage colony stimulating factor" or "GM CSF" or "embrogen" or "blastgen" or "blastogen" or "leucomax" or "tumour necrosis factor" or "tnf inhibit" or "etanercept" or "adalimumab" or "infliximab" or "certolizumab" or "golimumab" or "leukaemia inhibitory factor" or "lymphocyte immune therapy" or “pbmc” or “peripheral blood mononuclear cells”

END