UNIVERSITY OF BIRMINGHAM

RISK FACTORS AND MANAGEMENT OF MISCARRIAGE

By

JAYASISH GHOSH

A thesis submitted to the University of Birmingham for the degree of

DOCTOR OF PHILOSOPHY

Institute of Metabolism & Systems Research

College of Medical and Dental Studies

University of Birmingham

April 2021

UNIVERSITY OF
BIRMINGHAM

University of Birmingham Research Archive

e-theses repository

This unpublished thesis/dissertation is copyright of the author and/or third parties. The intellectual property rights of the author or third parties in respect of this work are as defined by The Copyright Designs and Patents Act 1988 or as modified by any successor legislation.

Any use made of information contained in this thesis/dissertation must be in accordance with that legislation and must be properly acknowledged. Further distribution or reproduction in any format is prohibited without the permission of the copyright holder.

Abstract

Miscarriage and pregnancy loss is unfortunately, an all-too-common early pregnancy complication for women and couples around the world. However, there are a great deal of unanswered questions about its causes and best practice surrounding its management. This thesis aims to improve the care of women and couples who have suffered from a miscarriage or have recurrent miscarriage. Using a systematic review and meta-analysis, a prospective cohort study, a systematic review and network meta-analysis and a narrative systematic overview review, the following has been found:

1. Hydrosalpinx is associated with higher pregnancy loss rates, particularly biochemical pregnancy loss in IVF pregnancies. Treatment of a hydrosalpinx may improve pregnancy outcomes, particularly using salpingectomy and tubal-conservational surgery.
2. Blocked fallopian tubes are common in the recurrent miscarriage population. Women with blocked fallopian tubes are at higher risk of pregnancy loss, have lower pregnancy rates and a lower chance of live births than women with patent tubes.
3. Suction curettage with cervical preparation is the best method for completing a miscarriage and expectant management is the worst method. Expectant management has the highest risk of serious complications and needing emergency surgery, medical methods have the highest risk of vomiting, diarrhoea and pyrexia.
4. Very few interventions have evidence of benefit for reducing miscarriage in both women who are symptomatic and asymptomatic of symptoms of miscarriage

5. The majority of evidence for interventions being of benefit or where no difference was shown, is very-low to moderate-quality and based on small numbers of trials and participants.

Dedication

This thesis is dedicated to my parents, Dr Aniruddha Ghosh and Mrs Meghla Ghosh. Without their countless sacrifices, enduring support and unconditional love over my entire life, I would not have started or finished this journey. Thank you so much from your ever grateful, loving son.

It is also dedicated to the next generation, my nephew and niece Kameron and Naya. May we leave the world a better place for you.

Acknowledgments

This body of work and thesis would not have been possible without the support, guidance and friendship of many people.

My first and largest thanks is to Professor Arri Coomarasamy, who first gave me this opportunity over 4 years ago and has taught me and guided me to develop not only in terms of academic skills, but as a person, a clinician, a leader and a change-maker. I probably do not yet know all the ways you have helped me develop.

Dr Ioannis D Gallos is another to whom I owe a great thanks, firstly as my SR who taught me how to be a registrar and then as my supervisor who taught me so much about evidence synthesis and thinking big.

Dr Justin J Chu, thanks for being my unofficial third supervisor, for being my life-mentor and friend/ big brother. Your advice is usually spot on. I promise I will try to listen to it, forgive me for doing an ECG.

Dr Rima Dhillon-Smith thank you for supervising my 5th chapter and all the guidance and advice. You are an inspiration to those that follow.

Thank you to Sister Oonagh Pickering and Miss Rachael Boothe for helping me with my trial and my recruitment. You greatly helped and picked me up when I needed it most. Thanks also to Wendy Gibson for keeping clinic together.

Thank you to Dr Adam J Devall, I don't how you find the time to help and support so many of the fellows. You are invaluable to us all.

Thank you to Dr Bala Karunakaran for guiding me through my first few months, I wouldn't have finished if I hadn't started well. Thanks also to Dr James Cheshire and Miss Ellie Thomas for putting such valued effort into advice on my chapters.

Thank you to the Nieto-Dixon's – Dr Thomas Nieto and Dr Hannah Nieto – thank you for looking after me and supporting me so much. You mean a great deal to me.

Thank you, Dr Catherine Dunlop, we started together and helped each other through and will finish together. It's been a much more enjoyable journey because of this.

Thank you to the many consultants at the Birmingham Women's Hospital who supported and helped me in many ways. Special mention to Dr Ellen Knox, Miss Pallavi Latthe, Miss Ruchira Singh, Miss Sam Pretlove, Dr Caroline Fox, Mrs Rima Rajkhowa, Dr Tracey Johnston, Miss Manjeet Shehmar, Dr Amy Wilbraham and of course Mr Philip Toozs-Hobson.

Miss Emily Gill, my girlfriend, thank you for your support and planning 90% of our meals this past year and putting up with me during lockdown and this write up.

Miss Nicola Farmer, my old housemate, thank you for putting up with me through this from the beginning.

Thank you to all my friends around the country whose support has been greatly appreciated.

Thank you to the UCB – the unofficial name for all the Coomarasamy team and other academics at the Birmingham Women's Hospital. Dr Amie Wilson, Dr Jennifer Tamblyn, Dr Preth Da Silva, Dr Paul Smith, Dr Fiona Mackie, Prof Abey Eapen, Dr Tina Verghese, Miss Elizabeth Quinlan-Jones, Dr William Parry-Smith, Dr Emily Colley, Dr Laurentiu Craciunas, Dr Hajra Khattak, Miss Helen Williams, Dr Nicole Pilarski, Dr Yealin Chung, Dr Pedro Melo, Dr Francis Muriti and Prof David Lissauer. You all made it as fun as it was!

Thank you to Tommy's the charity who funded my work and the people who support them.

Lastly, thank you to all the women who consented to be part of my trial and all my co-authors, couldn't have done it without you all.

TABLE OF CONTENTS

CHAPTER ONE: **1**

THESIS INTRODUCTION **1**

i) Anatomy, conception and the beginnings of pregnancy 1

ii) Miscarriage and recurrent miscarriage 3

iii) Management of miscarriage 10

iv) Risk factors and causes of miscarriage 15

v) Fallopian tube disease and miscarriage 20

vi) Detection of fallopian tube disease 23

vii) Aims and Objectives 29

viii) Summary of thesis 30

CHAPTER TWO: **32**

HYDROSALPINX & MISCARRIAGE: A SYSTEMATIC REVIEW AND META-ANALYSIS **32**

Abstract 34

Research question: 34

Design: 34

Results: 34

Conclusions: 34

Introduction 36

Materials and methods 38

Study selection 38

Validity assessment 39

Statistical analysis 40

Patient and Public Involvement 40

Results 41

Literature search 41

Study characteristics 42

Validity assessment 52

Pregnancy loss in women with and without hydrosalpinx 56

Pregnancy loss in women with and without treatment for hydrosalpinx 58

Biochemical pregnancy loss in women with and without hydrosalpinx 62

Biochemical pregnancy loss in women with and without treatment for hydrosalpinx .. 64

Clinical pregnancy loss in women with and without hydrosalpinx 66
Clinical pregnancy loss in women with and without treatment for hydrosalpinx..... 68
Ectopic pregnancy in women with and without hydrosalpinx 70
Ectopic pregnancy in women with and without treatment for hydrosalpinx 72
Discussion 74
Main findings..... 74
Strengths and limitations 74
Interpretation..... 78
Conclusion 80
CHAPTER THREE: 81
THE ROLE OF BLOCKED OR DAMANGED FALLOPIAN TUBES AND HYDROSALPINX IN RECURRENT MISCARRIAGE: A PROSPECTIVE COHORT STUDY OF PREVALENCE AND PROGNOSIS 81
Abstract..... 83
Research Question 83
Background 83
Methods 83
Results 84
Conclusion 84
Introduction 85
Material and methods 90
Study design 90
Statistical analysis 93
Ethical and other approvals 94
Results..... 95
Study participants 95
Baseline characteristics 98
Non-tubal abnormalities 101
Tubal abnormalities..... 103
Prognosis 103
Prognosis subgroup analyses 106
Discussion 110
Main findings..... 110

Strengths, limitations and difficulties 110
Interpretation 113
Conclusion 116
CHAPTER FOUR: 118
METHODS FOR MANAGEING MISCARRIAGE: A NETWORK META-ANALYSIS 118
Preamble 120
Abstract 120
Background 120
Objectives 120
Search methods 121
Selection criteria 121
Data collection and analysis 121
Main results 122
Authors' conclusions 124
Manuscript 125
CHAPTER FIVE: 127
PREVENTION AND MANAGEMENT OF MISCARRIAGE: A SYSTEMATIC NARRATIVE OVERVIEW REVIEW OF REVIEWS 127
Abstract 128
Research question 128
Design 128
Results 128
Conclusion 128
Introduction 129
Methods 130
Literature search 130
Inclusion and exclusion criteria 131
Study selection 132
Data extraction 133
Assessment of methodological quality of reviews 133
Data Presentation 134
Outcomes presented 135

Results 136
Study selection 136
Prevention of miscarriage in asymptomatic women 138
Prevention of miscarriage in symptomatic women 175
Management of miscarriage 182
Discussion 208
Main findings 208
Strengths and weaknesses 209
Interpretation 210
Conclusion 211
CHAPTER SIX: 212
THESIS CONCLUSIONS 212
i) Introduction 213
ii) What is the association between hydrosalpinx and miscarriage? 213
iii) What is the effect of treatment for hydrosalpinx on miscarriage? 215
iv) What is the prevalence of blocked tubes or a hydrosalpinx in the recurrent miscarriage population? 217
v) What is the prognosis of women with blocked tubes or a hydrosalpinx who are trying for a pregnancy? 218
vi) What is the best method of managing a miscarriage? 220
vii) What is the current body of evidence surrounding the management of miscarriage? 223
viii) Summary of findings of thesis 226
ix) Conclusion 229
REFERENCES 231
APPENDICES 250
Appendix 1: Protocol v1.1. for "The role of hydrosalpinx in recurrent miscarriage" 251
Appendix 2: Patient information sheet v1.1 for "The role of hydrosalpinx in recurrent miscarriage" 246
Appendix 3: Patient consent form v1.1 for "The role of hydrosalpinx in recurrent miscarriage" 271
Appendix 4: GP information sheet v1.1 for "The role of hydrosalpinx in recurrent miscarriage" 273

Appendix 5: Confirmation of sponsorship from The University of Birmingham for "The role of hydrosalpinx in recurrent miscarriage" 274

Appendix 6: IRAS form for "The role of hydrosalpinx in recurrent miscarriage" 275

Appendix 7: Confirmation of West Midlands Edgbaston Research Ethics Committee approval for "The role of hydrosalpinx in recurrent miscarriage" 289

Appendix 8: Confirmation of NHS Health Research Authority approval for "The role of hydrosalpinx in recurrent miscarriage" 316

Appendix 9: Confirmation of capacity and capability from Birmingham Women's and Children's NHS Foundation Trust Research and Development office for "The role of hydrosalpinx in recurrent miscarriage" 325

Appendix 10: Notification of request for amendment for "The role of hydrosalpinx in recurrent miscarriage" 329

Appendix 11: IRAS amendment form for "The role of hydrosalpinx in recurrent miscarriage" 331

Appendix 12 Protocol v1.2. for "The role of hydrosalpinx in recurrent miscarriage" 339

Appendix 13: Patient information sheet v1.3 for "The role of hydrosalpinx in recurrent miscarriage" 335

Appendix 14: Patient consent form v1.2 for "The role of hydrosalpinx in recurrent miscarriage" 361

Appendix 15: Confirmation NHS Health Research Authority approval for amendment for "The role of hydrosalpinx in recurrent miscarriage" 362

Appendix 16: Confirmation of registration with Clinicaltrial.gov for "The role of hydrosalpinx in recurrent miscarriage" 364

Appendix 17: Confirmation of approval from NIHR CRN as portfolio study for "The role of hydrosalpinx in recurrent miscarriage" 368

LIST OF FIGURES

Figure 1: Anatomical drawing of female reproductive organs from (1). The uterus and right ovary, seen from behind. The broad ligament has been spread out and the ovary drawn downward. 1

Figure 2: The pregnancy loss 'iceberg' from (16) showing pregnancy loss from conception to live birth, broken down into what percentage is due to implantation failure, pre-clinical biochemical pregnancy loss and clinical pregnancy loss. 9

Figure 3: A normal hystero-salpingogram showing bilateral passage of the radio opaque dye from the uterine cavity in the centre through both fallopian tubes and into the peritoneal cavity from (86). 25

Figure 4: A still image taken from a normal hystero-salpingo-contrast-sonogram from (87). This is a transverse view of the uterine fundus showing two echo-bright lines which represent the passage of the contrast media from the uterine cavity into the proximal cornual end of both fallopian tubes from..... 26

Figure 5: A still image picture from a laparoscopy and dye test from (88). The methylene blue which has been introduced into the uterus from the vagina via the cervix can be seen accumulating in the Pouch of Douglas in the centre of the image..... 27

Figure 6: Study selection process for the systematic review of hydrosalpinx and pregnancy loss 42

Figure 7: Meta-analysis of studies comparing pregnancy loss in women with hydrosalpinx to women with no hydrosalpinx 57

Figure 8: Meta-analysis of studies comparing pregnancy loss in women who had treatment (all interventions) for hydrosalpinx to women who did not undergo treatment for hydrosalpinx sub-grouped according to study type 59

Figure 9: Meta-analysis of studies comparing pregnancy loss in women who had treatment (all interventions) for hydrosalpinx to women who did not undergo treatment for hydrosalpinx sub-grouped according to intervention type..... 61

Figure 10: Meta-analysis of studies comparing biochemical pregnancy loss in women who had a hydrosalpinx to women who did not have a hydrosalpinx 63

Figure 11: Meta-analysis of studies comparing biochemical pregnancy loss in women who had treatment (all interventions) for hydrosalpinx to women who did not undergo treatment for hydrosalpinx 65
Figure 12: Meta-analysis of studies comparing clinical pregnancy loss in women who had a hydrosalpinx to women who did not have a hydrosalpinx 67
Figure 13: Meta-analysis of studies comparing clinical pregnancy loss in women who had treatment (all interventions) for hydrosalpinx to women who did not undergo treatment for hydrosalpinx 69
Figure 14: Meta-analysis of studies comparing ectopic pregnancy loss in women who had a hydrosalpinx to women who did not have a hydrosalpinx 71
Figure 15: Meta-analysis of studies comparing ectopic pregnancy loss in women who had treatment for hydrosalpinx to women who did not undergo treatment for hydrosalpinx sub grouped according to treatment type 73
Figure 16: Flow chart of participants during study 97
Figure 17: Flowchart of study selection process 137

LIST OF TABLES

Table 1: Terminology for classifying early pregnancy failure prior to viability for research purposes adapted from (5)..... 6
Table 2: Summary of thesis and structured questions for each chapter of this thesis 30
Table 3: Full study characteristics of all observational cohort studies looking at pregnancy loss in women with hydrosalpinx compared to women without hydrosalpinx..... 46
Table 4: Full study characteristics of all observational cohort studies and randomised controlled trials looking at pregnancy loss in women with untreated hydrosalpinx compared to women with treated hydrosalpinx 49
Table 5: Quality assessment of non-randomised cohort studies using the Newcastle-Ottawa Scale for cohort studies 53
Table 6: Quality assessment of randomised trials using the Cochrane risk of bias in randomised trials tool (RoB-2) 55
Table 7: ESHRE/ ESGE CONUTA classification system for congenital uterine anomalies from (125,126). 88
Table 8: USS features of adenomyosis described by the MUSA group from (128) 89
Table 9: Baseline characteristics of recruited women who had a HyCoSy, grouped according to result of HyCoSy 99
Table 10: Non-tubal abnormalities seen on HyCoSy, grouped according to result of HyCoSy 102
Table 11: Follow-up outcomes from women who completed a HyCoSy, no blocked tube versus at least one blocked tube, main analysis 105
Table 12: Follow-up outcomes from women who completed a HyCoSy, no blocked tubes versus one blocked tube, subgroup analysis 107
Table 13: Follow-up outcomes from women who completed a HyCoSy, no blocked tubes versus two blocked tubes, subgroup analysis..... 109
Table 14: Table of inclusion and exclusion criteria for review selection..... 132
Table 15: Table of information extracted from each included review..... 133
Table 16: Summary of reasons for exclusion of studies during full-text review 136

Table 17: Miscarriage and live birth outcomes from included systematic reviews looking at asymptomatic women..... 135
Table 18: Miscarriage and live birth outcomes from included systematic reviews looking at symptomatic women..... 163
Table 19: Outcomes from included systematic reviews looking at the management of miscarriage..... 177
Table 20: Summary of findings of thesis and structured questions and answers for each chapter of this thesis *226*

LIST OF ABBREVIATIONS

Ab2GP1 Anti beta 2 glycoprotein 1 antibodies

ACA Anticardiolipin antibodies

ACOG American College of Obstetricians and Gynaecologists

APS Antiphospholipid syndrome

ASRM American Society for Reproductive Medicine

ART Assisted reproductive treatment

BMI Body mass index

CDSR Cochrane Database of Systematic Reviews

CHM Chinese herbal medicines

CI Confidence interval

CMV Cytomegalovirus

COH Controlled ovarian stimulation/ hyperstimulation

CONUTA CONgenital UTerine Anomalies classification system

D&C Dilatation and curettage

EPL Early pregnancy loss

ESGE European Society of Gynaecological Endoscopy

ESHRE European Society of Human Reproduction and Embryology

EVA Electric vacuum aspiration

FDA Food and drug administration

FIGO International Federation of Gynaecology and Obstetrics

FSH Follicle stimulating hormone

FVL Factor V Leiden

HbA1c Glycated haemoglobin A1c

hCG Human chorionic gonadotrophin

HSV Herpes simplex virus

HIV Human immunodeficiency virus

HPV Human papillomavirus

HSG Hysterosalpingography

HyCoSy Hystero-salpingo-contrast-ultrasonography

IDEA International Deep Endometriosis Analysis group

IgG Immunoglobulin G

IgM Immunoglobulin M

IQR Interquartile range

ISUOG International Society of Ultrasound in Obstetrics & Gynaecology

IUI Intrauterine insemination

IVF In-vitro fertilisation

IVIG Intravenous immunoglobulin

LA Lupus anticoagulant

LH Luteinising hormone

LMWH Low molecular weight heparin

MD Mean difference

MeSH Medical subject heading

MMN Multiple micronutrient

MTHFR Methylenetetrahydrofolate reductase

MUSA Morphological Uterus Sonographic Assessment group

MVA Manual vacuum aspiration

NHS National Health Service

NICE National Institute of Health and Care Excellence

NIHR National Institute of Health Research

NMA Network meta-analysis

NOS Newcastle-Ottawa scale of quality assessment

OR Odds ratio

PALM-COEIN Polyp; Adenomyosis; Leiomyoma; Malignancy and hyperplasia; Coagulopathy; Ovulatory dysfunction; Endometrial; Iatrogenic; Not yet classified

PCOS Polycystic ovarian syndrome

PCO Polycystic ovary

PGE1 Prostaglandin E1

PGS Preimplantation genetic screening

POR Peto Odds Ratio

PTm ProthrombinG20210A

PUL Pregnancy of unknown location

RCT Randomised controlled trial

RCOG Royal College of Obstetricians and Gynaecologists

RoB-2 Cochrane collaboration risk of bias tool

RM Recurrent miscarriage

RPL Recurrent pregnancy loss

SD Standard deviation

SI Sexual intercourse

SMD Standardised mean difference

SUCRA Surface area Under the Cumulative Ranking

UFH Unfractionated heparin

UK United Kingdom

UPSI Unprotected sexual intercourse

USA United States of America

USS Ultrasound scan

WHO World Health Organisation

CHAPTER ONE:

THESIS INTRODUCTION

A sperm fertilises an egg in the fallopian tube, forming a zygote. The zygote will begin to divide firstly into two cells, then four, and so the cycle of reproduction has begun. The early development from two gametes, to the zygote stage and to a recognisable fetus is well documented and not the topic of this thesis. However, its brief discussion here, and about basic anatomy is necessary as a prelude to discussion about miscarriage, which is the subject of this thesis.

i) Anatomy, conception and the beginnings of pregnancy

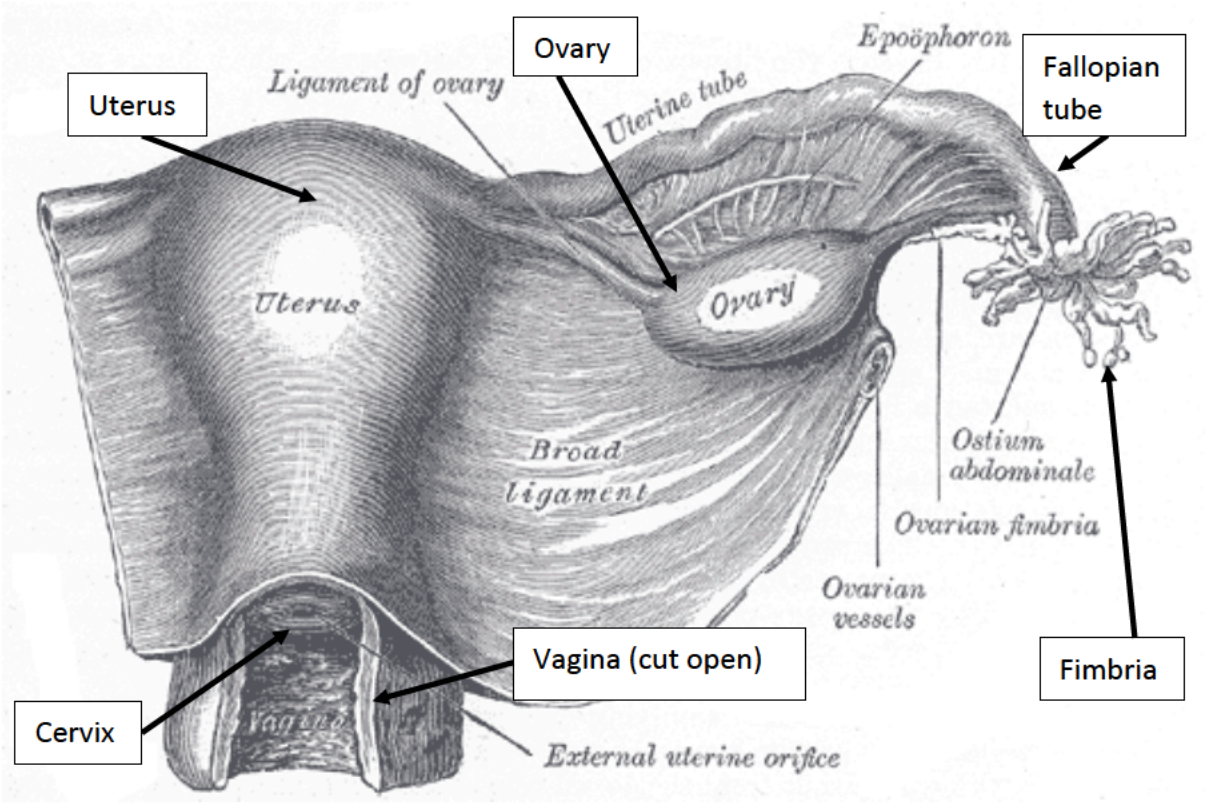


Figure 1: Anatomical drawing of female reproductive organs from (1). The u*terus and right ovary, seen from behind. The broad ligament has been spread out and the ovary drawn downward.*

The female reproductive organs comprise of the cervix, uterus, fallopian tubes and ovaries (Figure 1) The female reproductive process can be considered to b egin with the menstrual cycle, which itself begins with the shedding of the glandular epithelial

endometrium which lines the inner cavity of the uterus. Following the endometrial shedding, under the influence of oestrogen from the granulosa cells of the ovary, the endometrium will proliferate again, ready to accept a fertilised gamete.

Parallel to the endometrial development, multiple oocytes in primordial follicles, which are in a dormant state in the ovary, begin to mature under the hormonal influence of the anterior pituitary derived, follicle stimulating hormone (FSH). These primordial follicles will mature and grow until a dominant Graafian follicle emerges. Usually around day 14 of a regular 28-day menstrual cycle, ovulation occurs, triggered by a luteinising hormone (LH) surge also from the anterior pituitary gland. The dominant follicle releases the mature oocyte through the surface of the ovary into the abdominal cavity. The fimbriae of the fallopian tube then sweep the oocyte into the inner lumen of the tube. Cilia, which line the inner lumen, help to move the oocyte towards the uterine cavity.

Meanwhile a motile sperm, which has travelled via the cervix from the vagina and through the uterus will meet the oocyte in the ampulla of the fallopian tube. Should fertilisation occur, a zygote is formed and the cilia of the fallopian tube continue to usher the zygote towards the endometrium which has been proliferating as described before. The zygote will be undergoing mitosis and growing into a morula and eventually into a blastocyst. By the blastocyst stage, the cells will have divided into two distinct groups, the trophectodermal cells and the inner cell mass. After reaching the uterine cavity, the blastocyst hatches out, with the trophectodermal cells turning into trophoblast cells, which will invade the endometrium, and

eventually become the placenta. This is implantation and usually occurs seven to ten days after ovulation.

Meanwhile the inner cell mass will have begun to divide and differentiate into an embryo moving from the germinal stage into the embryonic stage of development. Gastrulation will occur, followed by neurolation and then organogenesis where the organ systems we recognise in an adult are formed. After the majority of organogenesis has occurred the fetus will grow eventually reaching viability at approximately 24 weeks gestation.

ii) Miscarriage and recurrent miscarriage

During these initial stages of pregnancy, problems can occur at many points with the development of the pregnancy, often resulting in miscarriage and pregnancy loss. Before proceeding further, it is important to define what we mean by miscarriage and recurrent miscarriage and to briefly discuss the terminology surrounding miscarriage and how it may vary across the world and how it evolved.

The terminology surrounding miscarriage has evolved over time and there are cultural, linguistic, legal and technological reasons for this. The term abortion, from the Latin “abortio”, meaning “untimely birth” has been used for hundreds of years in the English language. It was previously synonymous with miscarriage, as they were difficult to distinguish clinically, and not until the Abortion Act 1967 (2), when termination of pregnancy was legalised, were

women less afraid of being criminalised when seeking medical attention for either and so there became a need for separate terminology (3). The Abortion Act 1967 (2) also brought about a cultural change whereby there was less social stigma surrounding termination of pregnancy (3). In British medical literature, Professor Richard Beard instigated a cultural shift from the use of "abortion" to "miscarriage" in the late twentieth century, to describe spontaneous pregnancy loss, in his letter to the Lancet in 1985 (4). This was reflected in the sharp decrease in the use of "abortion" in favour of "miscarriage" when describing spontaneous early pregnancy loss in the British Journal of Obstetrics and Gynaecology, the British Medical Journal and the Lancet from the mid 1980's onwards (3). The advent and continued development of medical ultrasound and its use in early pregnancy since the mid 1970s has also brought about the need for more extensive terminology to differentiate between different pathologies that were now distinguishable (3). The above only describes the evolution of the language around pregnancy loss in the United Kingdom. Around the world, over the past 40 years, different terminologies have organically arisen, each influenced by local linguistic, cultural and legal factors. It is because of this, that differences in definitions exist around the world and we will now discuss some of these definitions. It also highlights the importance of consensus statements so that there can be a convergence of language and terms in an increasingly connected and collaborative world.

The Royal College of Obstetricians and Gynaecologists (RCOG), in their 2011 green-top guideline number 17 (5), defined miscarriage as:

"the spontaneous loss of pregnancy before the foetus reaches viability. The term therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation. It should be noted that advances in neonatal care have resulted in a small number of babies surviving birth before 24 weeks of gestation."

Whilst the American College of Obstetricians and Gynaecologists (ACOG) use the term early pregnancy loss (EPL) instead of miscarriage, choosing to be more specific to losses in the first trimester and their definition from their 2018 practice bulletin number 200 (6) was:

"a nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or foetus without foetal heart activity within the first 12 weeks of gestation. In the first trimester, the terms miscarriage, spontaneous abortion, and early pregnancy loss are used interchangeably, and there is no consensus on terminology in the literature"

The European Society of Human Reproduction and Embryology (ESHRE) prefer to use the term pregnancy loss instead of miscarriage and use the previously mentioned RCOG definition in their recurrent pregnancy loss guideline (7) published in November 2017 but add the caveat of:

"…different definitions apply in different countries."

ESHRE have also used the following definition in a consensus statement (8) from their Early Pregnancy Interest Group in 2015:

"Under normal, non-neoplastic conditions, human chorionic gonadotrophin (hCG) is exclusively produced by the syncytiotrophoblast. It follows logically that a pregnancy loss

is the spontaneous demise of a pregnancy, which has been confirmed by at least two positive b-hCGs in the serum or urine."

As we can see, there is variety not just in definitions but also in terminology used, as acknowledged by the ACOG and ESHRE. Probably the most thorough discussion over terminology is by ESHRE in their 2015 consensus statement (8) by Kolte et al. is adapted from this consensus statement and for this thesis I will be using this terminology for consistency and clarity.

Table 1: Terminology for classifying early pregnancy failure prior to viability for research purposes adapted from (8)

Term	**Definition or description**
Pregnancy loss	Spontaneous pregnancy demise
Early pregnancy loss	Spontaneous pregnancy demise before 10 weeks of gestational age (before 8th developmental week)
Non-visualized pregnancy loss	Spontaneous pregnancy demise based on decreasing serum or urinary b-hCG levels and non-localization on ultrasound, if performed
Biochemical pregnancy loss	Spontaneous pregnancy demise based on decreasing serum or urinary b-hCG levels, without an ultrasound evaluation
Resolved pregnancy loss of unknown location (resolved PUL)	Pregnancy demise not visualized on transvaginal ultrasound with resolution of serum b-hCG after expectant management or after uterine evacuation without chorionic villi on histology
Treated pregnancy loss of unknown location (treated PUL)	Pregnancy demise not visualized on transvaginal ultrasound with resolution of serum b-hCG after medical management
Miscarriage	Intrauterine pregnancy demise confirmed by ultrasound or histology
Early miscarriage	Intrauterine pregnancy loss ,10 weeks' size on ultrasound
Anembryonic (empty sac) miscarriage	Intrauterine pregnancy loss with a gestational sac but without a yolk sac or an embryo on ultrasound

Yolk sac miscarriage	Intrauterine pregnancy loss with a gestational sac and yolk sac, without an embryo on ultrasound
Embryonic miscarriage	Intrauterine pregnancy loss with an embryo without cardiac activity on ultrasound
Fetal miscarriage	Pregnancy loss ≥10 weeks' size with a fetus (≥33 mm) on ultrasound
Ectopic pregnancy	Ultrasonic or surgical visualization of a pregnancy outside of the endometrial cavity

Moving onto recurrent miscarriage, here also, there is variation in the definition. The RCOG defined it in their 2011 green-top guideline number 17 (5) as:

> *"…the loss of three or more consecutive pregnancies…"*

It should be noted that this RCOG guideline has been due for review since 2014 and an updated version is currently pending. ACOG in their 2001 practice bulletin on the management of recurrent early pregnancy loss (9) defined recurrent miscarriage as:

> *"Recurrent pregnancy loss typically is defined as two or three or more consecutive pregnancy losses"*

Meanwhile the ESHRE early pregnancy guideline development group decided in their recurrent pregnancy loss guideline (7) in 2017 on a broader definition of:

> *"A diagnosis of Recurrent Pregnancy Loss (RPL) could be considered after the loss of two or more pregnancies."*

For the purposes of this thesis, I shall be using the ESHRE definition of recurrent miscarriage.

Now definitions and terminology have been discussed, I will move onto discussing the disease burden of miscarriage to establish why this is an important area of research. Miscarriage is

common, it is the most frequently occurring complication of pregnancy (10) and its management carries with it a great burden both to the women and couples it affects and the National Health Service (NHS). One in five pregnancies miscarries, which equates to over 250,000 miscarriages a year in the UK (11,12). There were 36,154 hospital admissions in the financial year of 2018-2019 (13) related to miscarriage. The financial cost for NHS trusts and Foundation Trusts for treating threatened or spontaneous miscarriage with and without interventions was £30,922,982 in the financial year of 2018-2019 with each episode costing on average £2097 if there was an intervention or £575 if there was not (14).

Just as important as the physical and resource costs of miscarriage, is the psychological impact on both women and couples who suffer from it. Women can develop significant depression, anxiety and even post-traumatic stress symptoms following a miscarriage (15) whilst their partners can also exhibit depression and anxiety (16) . These symptoms and diagnoses are also not short lasting, miscarriage is a significant source of psychological morbidity for these women and couples and its effects have been shown to last for a year (17).

Miscarriage of course also causes physical health problems. Abdominal and pelvic pain or cramping which can be severe, haemorrhage requiring emergency treatment and surgery, infections requiring antibiotic treatment are the well described morbidities of miscarriage. Although rare (circa one percent or less), severe haemorrhage or infection can also require admission to a hospital (18).

The estimates for the numbers of miscarriages listed earlier may in fact be an underestimation. It has been estimated that up to 70% of conceptions may result in a pregnancy loss but due to the very early nature of up to 60% of these, the pregnancy may not have been recognised by the woman (19) suggesting this maybe a larger problem than official statistics can detect (Figure 2).

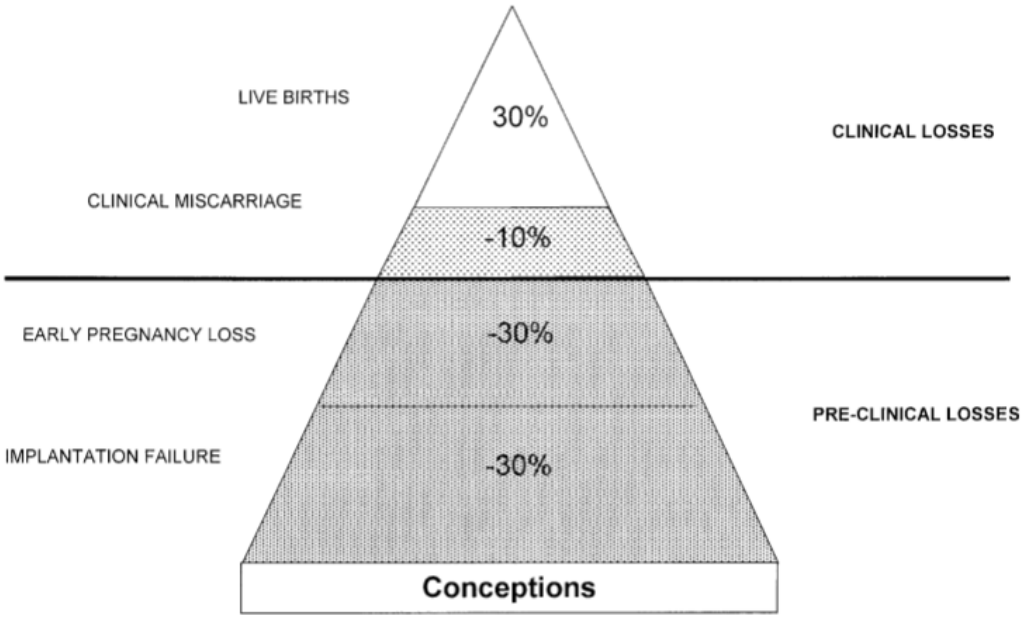


Figure 2: The pregnancy loss 'iceberg' from (19) *showing pregnancy loss from conception to live birth, broken down into what percentage is due to implantation failure, pre-clinical biochemical pregnancy loss and clinical pregnancy loss.*

As many miscarriages are in fact unrecognised, particularly if they are early (four to six weeks after the last menstrual period), miscarriage data that is currently available may be unreliable. The reasons for this are likely to be multifactorial. For example, women with irregular periods may not notice any change from their usual menstrual cycle. The increasing prevalence of obesity could hide physical signs of pregnancy, although this is unlikely in early pregnancy.

Even in women with regular periods, a miscarriage could conceivably be passed off by the woman as a late or heavy period and not given much extra thought. The classical early pregnancy symptoms of fatigue, nausea, vomiting, breast soreness and others (20) may not be experienced by all women (21) which will undoubtedly also contribute. There will also be mental health reasons why a small proportion may also not recognise they are pregnant (21).

Related to this is that, even when pregnancies are recognised by the women, they are often not reported to family medicine practitioners or early pregnancy units. This is likely to be as miscarriage is so common and at this gestation there is usually no need for treatment to complete the miscarriage, there is a perception that there are no treatments to prevent the miscarriage (which is often the case) and no benefit of other medical interventions such as an ultrasound scan. Furthermore, investigations for recurrent miscarriage often do not occur until there are three concurrent miscarriages, for example in the U.K (5), so there is no perceived benefit from reporting the miscarriage to medical services.

As we can see, the total encumbrance of individual patient and the system-wide burden of miscarriage, including the physical, psychological, organisational and economic costs is great.

iii) Management of miscarriage

Miscarriage can be managed in a number of different ways. For most of human history, the only available treatment would have been expectant or conservative treatment, allowing the

body to expel pregnancy tissues naturally. The practice of surgical curettage to scrape pregnancy tissues after a miscarriage was first described in the 19th century (22). Often combined with manual dilatation, hence called dilatation and curettage (D&C), its use has over recent decades fallen out of favour in high resource settings due to concerns over the increased risk of subsequent pre-term birth (23) and other complications such as perforation and Asherman's Syndrome (24). Electric vacuum aspiration (EVA) or suction curettage is said to have been invented in 1958 by Drs Wu Yuantai and Wu Xianzhen in China (25) but only published in their native language in the Chinese Journal of Obstetrics and Gynaecology. Its spread to the United Kingdom is mainly credited to Dr Dorothy Kerslake after she described the technique in 1967 (26,27). Manual vacuum aspiration (MVA), a form of suction curettage using the negative pressure of a large syringe was first designed and described by Harvey Karman in 1972 (28). The RCOG lists bleeding, infection, retained pregnancy tissue, need for repeat procedure, intrauterine adhesions, perforation, cervical trauma and need for laparoscopy or laparotomy in their consent advice number ten document as recognised risks for surgical management of miscarriage which women should be counselled about during the consent process (29). Serious complications such as perforation are uncommon (up to 1 in 1000 women) (30). The risk of intrauterine adhesions from surgical evacuation is quoted as 16.3%-18.5%, however, the majority of these were considered to be mild and their clinical significance unknown (31).

Intrauterine adhesions after curettage were first described in 1894 (32). Further research by Joseph Asherman in 1948 on the aetiology and prevalence resulted in the eponymous name

Asherman Syndrome (33). Excessive curettage causing the destruction of the basal endometrium and the subsequent opposition of the uterine walls as the basal endometrium heals resulting in adherence and adhesions, is thought to be the most common cause (34). Signs and symptoms may include menstrual abnormalities such as amenorrhea, oligomenorrhea, cyclical lower abdominal pain, infertility or recurrent miscarriage (35). Its prevalence has been quoted as 4:10,000 (36). However, it may go unrecognised or unreported in women who are unconcerned with conception or its symptoms (37) and so its true prevalence may be higher. The RCOG state there is no significant difference in long-term fertility outcomes between the different treatment options of expectant, medical or surgical management of miscarriage although they caveat this statement mentioning that the number of studies and women studied was limited (29).

In the mid-1980s a synthetic prostaglandin E1 (PGE1) analogue called misoprostol was produced by Pharmacia, a Swedish pharmaceutical and biotechnology company (38). Initially used to treat gastric ulcers caused by non-steroidal anti-inflammatory drugs, its unregistered use soon began in reproductive circles for the treatment of miscarriage, intrauterine fetal demise and induction of labour. Misoprostol was found to be effective by clinicians at inducing contractions in a uterus, softening the cervix before instrumentation of the uterus (38). It also had the advantages of being cheap and heat-stable (38). In 1998, mifepristone, an anti-progestin, was first approved for use in France and the UK followed with approval in 1991 (39). Its use in combination with misoprostol was first approved by the Food and Drug Administration (FDA) in the United States of America (USA) in 2003 (40). Both misoprostol and

mifepristone are now recognised by the World Health Organisation (WHO) as essential medications (41) having been introduced in 2005 (42).

There are therefore broadly three categories of treatment for miscarriage; expectant or conservative, medical with misoprostol alone or in combination with mifepristone, and surgical options such as D&C, EVA and MVA. The National Institute of Health and Care Excellence (NICE) in their 2012 guideline on the management of miscarriage (43) recommend expectant management for seven to 14 days as a first line treatment if clinically suitable. And either medical or surgical treatment as a second line treatment but only if the woman is agreeable to this course of action and it is clinically appropriate.

The decision-making process which women use to decide on which management option to proceed with, is undoubtedly very individualised but there will be common themes. I would imagine these to be highly dependent on the woman's individual circumstances such as physical and mental health, previous experiences, future fertility considerations, social and emotional support, religious or cultural beliefs, work and caring responsibilities, access to healthcare and transportation, financial situation and the counselling received from their healthcare provider. All of these factors will interplay to varying amounts to allow the woman to hopefully make the correct decision for her as an individual.

There is RCT evidence for clinical outcomes on expectant management versus medical versus surgical management but it is interesting to note that the choice of 13 outcomes that NICE prioritised were directly chosen by the guideline development group (43). This group does contain two lay members; however, no formal Delphi process was undertaken to establish the outcome priorities of the women who are being treated on the basis of this guideline. This might be a reflection of the fact that whilst there have been incremental evidence updates to this guideline, it is in essence nearly nine years since it was published and many more since work on it began and such importance of patient and public involvement in medical research has developed since. Of the 13 outcomes examined, only mental health, anxiety and satisfaction are priority outcomes which are not physical health related or clinical outcome measures. We simply do not know what the outcomes that are a priority for women are, when deciding upon their preferred treatment and this is something that should be established before this guidance is formally updated so it can inform the review questions that are answered. This effort maybe hindered by the fact that the studies reported in this guidance are not recent and often small and of poor quality so the evidence may not exist to provide guidance. The NICE recommendation of expectant management for seven to 14 days as first-line management is primarily on the basis that health-economic analysis showed expectant management to be the most cost-effective treatment modality (43). NICE then go on to recommend that women should have a choice of all treatment options should expectant management fail. It is reassuring to note that these recommendations are caveated to ensure that women are not forced into expectant management if they deem it unacceptable and that consideration is given to previous adverse experiences. Whilst there should be health-economic considerations of recommendations, due to the resource limitations of a completely

publicly funded nationalised healthcare system provider, we must also consider a holistic and individualised approach when counselling and offering treatment to these women. What is lacking in this area is not correct and up to date guidance but rather patient-centred evidence to allow clinicians to delivery personalised care.

iv) Risk factors and causes of miscarriage

We have discussed so far about what miscarriage is, the disease burden, the terminology involved and how it can be treated but it is also important to understand why it occurs especially in the context of recurrent miscarriage. Most miscarriages are in the first trimester (44). Most miscarriages which happen in the first 12 weeks of a pregnancy are because of sporadic chromosomal abnormalities (45). These abnormalities account for about 50% of first-trimester pregnancy losses (45). The vast majority of these abnormalities are numerical abnormalities (86%) such as the trisomy's of chromosome 21, 18 and 13, which cause Down's, Edward's or Patau's syndrome respectively (45) and are known as aneuploidies. A smaller percentage of abnormalities (6%), are caused by structural anomalies which are known as either balanced or unbalanced translocations (45). The rest (8%) are caused by other genetic problems, for example chromosome mosaicism (45).

Often related to chromosomal abnormalities is the risk factor of female age. Indeed, increasing female age is a risk factor for many adverse pregnancy related outcomes. It is associated with pre-eclampsia, hypertension in pregnancy, gestational diabetes, placenta praevia, placental abruption, post-partum haemorrhage, operative vaginal delivery,

caesarean section and pre-term delivery (46). However, specific to this thesis, the risk of miscarriage is 8.9% in women aged 20-24 but rises to 74.7% in women aged 45 years and above with a progressive increase in risk between these ages (47).

The risk of miscarriage also varies greatly according to the gestational age of the pregnancy. The risk is highest, earliest in pregnancy, at five weeks of gestation, with estimates of the weekly miscarriage rate per 1000 woman-weeks of 32.79 (95% CI 10.65-76.51) (48), 36.70 (95% CI 4.44-132.56) (49) and 29.63 (95% CI 3.59-107.03) (50) across three studies. This contrasts with estimates at 14 weeks of gestation by the same measure above, of 4.38 (95% CI 3.56–5.33) (48), 3.99 (95% CI 2.71–5.66) (49) and 8.15 (95% CI 3.28–16.8) (50) across the same three studies.

Increasing body mass index (BMI) is also associated poor reproductive outcomes. Obesity, defined as a BMI of greater than and including 30 kg/m^2, is associated with an increased risk of obstetric complications such as preterm delivery, fetal macrosomia, pre-eclampsia, gestational diabetes and instrumental delivery and caesarean section (51–53). Specific to fertility, obesity is associated with menstrual cycle irregularities including anovulation (54). Time to pregnancy is increased in women with a BMI greater than 25 kg/m^2 and progressively worsens the higher the BMI (55). And obesity significantly increases the risk of both miscarriage and recurrent miscarriage (56).

Smoking of tobacco products is detrimental to general health but it is also harmful to a woman's fertility (57). Current smokers, those who had previously smoked or had tobacco smoke exposure have decreased serum oestradiol concentrations, decreased numbers of oocytes retrieved and embryos during assisted conception and decreased gonadotrophin stimulated ovarian function (58). Previous and current smokers also have an increased risk of early menopause (59,60) with menopause occurring at a younger age in women who smoke (one to four years earlier) (59,61). Smoking is also associated with both sporadic and recurrent miscarriage (62). It is associated with a significantly increased risk of miscarriage in women undergoing assisted conception (63) and environmental tobacco smoke (more commonly known as passive smoking) is associated with a significantly increased risk of recurrent miscarriage (62).

The relationship between caffeine consumption and miscarriage is less well evidenced and agreed upon. There is evidence of an adverse dose-dependent relationship between caffeine consumption during the periconception period and earlier gestations with unexplained recurrent miscarriage (64), late miscarriage and still birth (65) and low birth weight and childhood acute leukaemia (66) but this has yet to be reflected in national guidance.

Alcohol can also have a detrimental effect on pregnancy. There is a significantly increased risk of early miscarriage with the consumption of greater than four units of alcoholic drinks per week and this is particularly the case before ten weeks of gestation; however, the association

with miscarriage is not as strong later in pregnancy (7). The relationship between recurrent miscarriage and alcohol consumption has currently not been investigated (67).

Probably the most well-known risk factor for miscarriage is the acquired thrombophilia antiphospholipid syndrome (APS) (68). It is diagnosed according to the revised 1999 Sapporo criteria (69) and requires one clinical criterion, of which the one relevant to this thesis, is three or more unexplained consecutive spontaneous miscarriages. The diagnosis also requires one laboratory criterion of two positive results of either lupus anticoagulant (LA), anti-cardiolipin antibodies (ACA) IgG and/or IgM or anti beta-2 glycoprotein-1 (Ab2GP1) IgG and/ or IgM, greater than 12 weeks apart. However, a more recent cohort study (70) showed there was no increase in the diagnostic yield after three versus two miscarriages; therefore, APS can be tested and diagnosed after two miscarriages.

The relationship between miscarriage and inherited thrombophilias are more complex. Factor V Leiden (FVL) carriers and sufferers are significantly more likely to suffer from a miscarriage than women who don't have the mutation (71,72). There is also an association between prothrombin gene mutation and miscarriage although only in women with 2 or more miscarriages, not three or more (73). The same study found no significant association with protein C, protein S and antithrombin III deficiencies and miscarriage (73). Other studies found women with RPL were more likely to have protein S deficiency but not protein C deficiency, FVL or prothrombin gene mutation (74), and that activated protein C resistance maybe more common in women previous loss of a pregnancy (75). Overall, the evidence is conflicting.

Metabolic and endocrine disease, particularly when uncontrolled are associated with miscarriage. The two most frequently associated with miscarriage are diabetes mellitus and hypothyroidism. Women with high haemoglobin A1c (HbA1c) levels, which is a marker of diabetes mellitus and gives an indication of the control of the disease, are at increased risk of miscarriage (76). Furthermore, abnormal glucose tolerance test results are much more common in the recurrent miscarriage population compared to controls and treatment with metformin, an insulin sensitizer and treatment for type two diabetes mellitus improves the miscarriage rate in this group (77). It should be noted, that well controlled diabetes mellitus does not increase the risk of miscarriage (78).

Similarly, for thyroid disease, suboptimal thyroid function is related to a host of adverse pregnancy outcomes. These include miscarriage but also preterm birth, low birth weights, placental abruption and postpartum haemorrhage (79,80). However, adequate treatment minimizes these risks (81).

Almost any severe systemic infection can cause a miscarriage. In particular, however, influenza, cytomegalovirus (CMV), human immunodeficiency virus (HIV), malaria, brucellosis dengue fever and bacterial vaginosis are associated with an increase in the risk of miscarriage (82). There is conflicting evidence regarding other pathogens such as human papillomavirus (HPV), Hepatitis B, herpes simplex virus (HSV), *Chlamydia trachomatis*, parvovirus B19 and

Toxoplasma gondii, with no increase in risk shown by some studies and others indicating an increase in the risk of miscarriage (82).

Anatomical uterine anomalies can also affect miscarriage. The prevalence of uterine anomalies is approximately five times higher in the recurrent miscarriage population compared to an unselected population (83). Miscarriage rates have been shown to be significantly higher in women with congenital uterine anomalies compared to women without anomalies (84). This is particularly the case with septate or bicornuate uteri (5).

Having discussed the impact of genetic problems such as aneuploidies, translocations and mosaicism, lifestyle factors such as BMI, smoking, caffeine and alcohol, other issues such as age and anatomical anomalies and finally medical conditions such as thrombophilias, metabolic and endocrine conditions and infections we have taken a thorough journey through the multitude of risk factors for miscarriage. However, despite very thorough investigation for the above risk factors, a significant proportion of women with recurrent miscarriage will be labelled as unexplained and be left with no definitive answers, treatments or sometimes sadly, hope (5).

v) Fallopian tube disease and miscarriage

The fallopian tubes are of paramount important to pregnancy as we have discussed earlier, especially as they are the usually the site of fertilisation. Named for Gabriel Fallopius (85), a

16th century Italian anatomist and Catholic priest, they transmit the ovum released at ovulation from a ruptured graafian follicle, towards the uterus, by the action of cilia on their inner lumen which is lined by columnar epithelium. Fertilisation of the ovum usually occurs in the ampulla of the fallopian tube. Fallopian tubes are usually ten to 13 centimetres in length and when healthy are less than 1.2 centimetre in diameter (86), yet they can be easily damaged by a variety of conditions.

Probably the most well-known cause of fallopian tube damage is infection. *Chlamydia trachomatis* is the most common sexually transmitted infection in the UK with 131,269 new diagnoses in the 15 to 24-year-old age groups alone, in the U.K., in the calendar year of 2018 (87). Untreated *C. trachomatis* infection in pregnancy may increase the risk of miscarriage, preterm birth, low birth weight and stillbirth (82,88,89). *Neisseria Gonorrhoea* is the second most common sexually transmitted infection in the UK (87) and the most common in the world (90). For both of these, the sequelae of infection include pelvic inflammatory disease, ectopic pregnancy, chronic pelvic pain and tubal factor infertility (91,92). Infections which cause tubal damage can also occur after a miscarriage, termination of pregnancy, puerperal sepsis or insertion of an intrauterine device (93). The fallopian tubes can also be damaged by endometriosis and pelvic surgery, both of which can cause adhesions between pelvic organs (93).

A severe form of tubal damage is when the tube is blocked distally and filled with fluid, a condition called hydrosalpinx. They are classically caused by ascending infections from the

lower genital tract, such as those described above, causing the tubes to appear swollen and enlarged (94). Hydrosalpinx is associated with a dramatic reduction in the chances of a live birth with assisted reproductive techniques (95). This is explained by reduced implantation chances and increased pregnancy losses in the presence of a hydrosalpinx (95). It is therefore strongly recommended that hydrosalpinges are removed or treated by tubal surgery before in-vitro fertilisation (IVF) treatment (96).

The reasons for the impact of hydrosalpinx on implantation again have not been well established. It has been shown in a small case series that, in hydrosalpinges, the peristaltic frequency was higher, the amplitude of peristalsis was lower, as was the width of the lumen of the tube in its passive state compared to the fallopian tubes of healthy volunteers (97). This in turn failed to cause the transport of a fluid bolus towards the uterine cavity which in turn adversely affects the normal pattern of flow of fluids between the cervix, uterus and tubes. This gives rise to a reflux phenomenon which could move embryos away from the implantation site reducing implantation rates. Tubal fluid could also act to impede implantation in the tubes as a natural mechanism to prevent tubal ectopic pregnancy and the altered flow of this fluid could in theory also effect implantation. An alternative mechanical flushing effect has also been proposed (98). A simpler explanation could also be mechanical impedance of implantation due to the surface tension created by a fluid interface caused by the fluid from a hydrosalpinx accumulating inside the cavity as it is unable to flow into the peritoneal cavity via the fimbrial end due to distal occlusion (99). This is expanded upon by Lu in 2013, who found excessive non-toxic intrauterine fluid, delayed implantation and slowed

the normal development of embryos in murine models (100). The adverse impact of hydrosalpinges on developing pregnancies may not just be due to mechanical causes but direct toxicity of the fluid. Hydrosalpinx fluid has been shown to have an adverse effect on developing murine embryos in a dose dependant relationship (101). It has also been proposed that hydrosalpinx fluid may produce a chronic alteration of the intrauterine environment and the endometrial receptivity (102). This could be related to alterations of the complex immunological processes that govern implantation.

It has been suggested that hydrosalpinx may also have a causative role in miscarriage (103). The biological rationale for this possible increase in pregnancy losses is not yet well understood and there is likely to be some overlap with the proposed mechanisms above for the negative impact on implantation. It has been postulated that the hydrosalpinx fluid may be embryotoxic as it can include micro-organisms, endotoxins, cytokines and free radicals causing oxidative stress (101,104,105). This fluid may therefore alter the endometrial receptivity causing a disturbed cytokine cascade, which impedes development of the pregnancy (106). Additionally, as the fallopian tube is occluded distally, the hydrosalpinx fluid may drain into the endometrial cavity having a flushing effect on the developing embryo (98).

vi) Detection of fallopian tube disease

The investigation of suspected tubal disease is currently recommended only for women with subfertility. Women often have laparoscopy or hysterosalpingography (HSG) for tubal assessment (96). Women who are not known to have comorbidities (such as pelvic

inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered HSG to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion, and it is less invasive and makes more efficient use of resources than laparoscopy (96).

A HSG involves the passage of a radio-opaque contrast media through the female cervix whilst simultaneously taking serial radiographs to examine the patency and free spill of the media into the abdominal cavity (Figure 3). It requires radiographers, specialist radiographic equipment and exposure to radiation. Furthermore, an HSG is performed in a radiology department and requires a radiologist to interpret them.

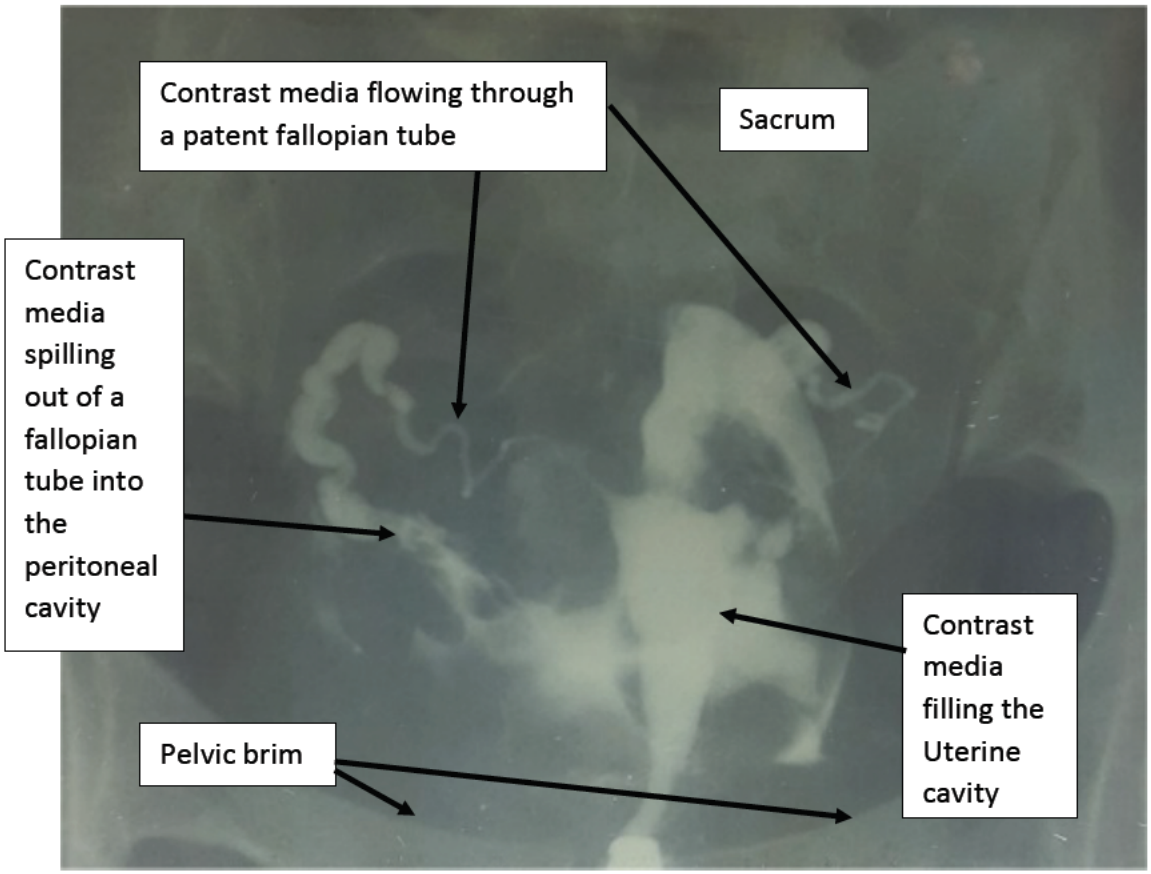
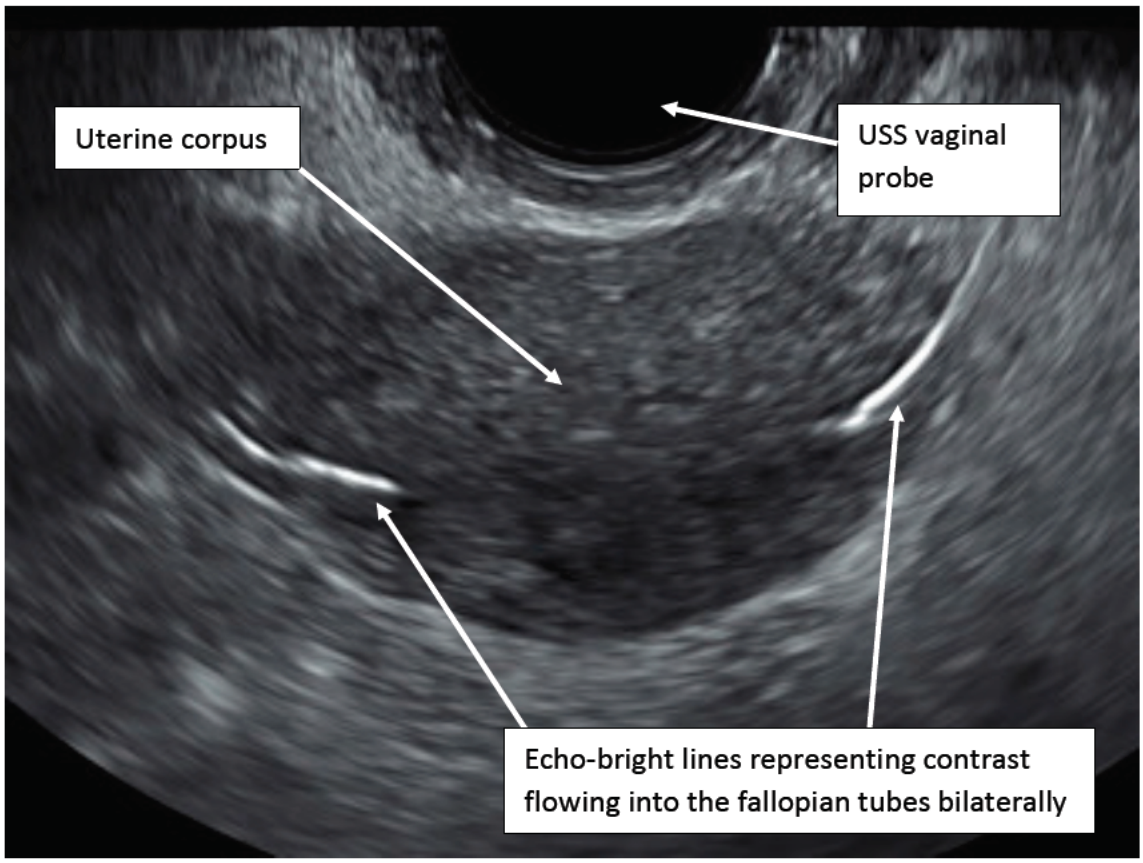


Figure 3: A normal hystero-salpingogram showing bilateral passage of the radio opaque dye from the uterine cavity in the centre through both fallopian tubes and into the peritoneal cavity from (107).

Where appropriate expertise is available, screening for tubal occlusion using hystero-salpingo-contrast-ultrasonography (HyCoSy) can be considered because it is an effective alternative to HSG for women who are not known to have comorbidities (96). A HyCoSy is an outpatient procedure which only requires a special contrast media and an ultrasound machine which is usually present in many gynaecological out-patient departments. HyCoSy is performed at the same time as a pelvic ultrasound, which is recommended for both women with subfertility or recurrent miscarriages (5,96). The contrast media is injected through the cervix and its flow

into the uterus and out through the fallopian tubes is tracked in real time using the ultrasound machine to detect tubal patency and pathology (Figure 4).

Figure 4: A still image taken from a normal hystero-salpingo-contrast-sonogram from (108). *This is a transverse view of the uterine fundus showing two echo-bright lines which represent the passage of the contrast media from the uterine cavity into the proximal cornual end of both fallopian tubes.*



Laparoscopy is an invasive operative investigation where by a fibre optic camera, inserted through the umbilicus, is used to directly visualise the passage of dye through the fallopian tubes thereby confirming their patency and function whilst the patient is under general anaesthesia (Figure 5). Women who are thought to have gynaecological comorbidities should be offered laparoscopy and dye testing so that tubal and other pelvic pathology can be assessed and treated at the same time (96).

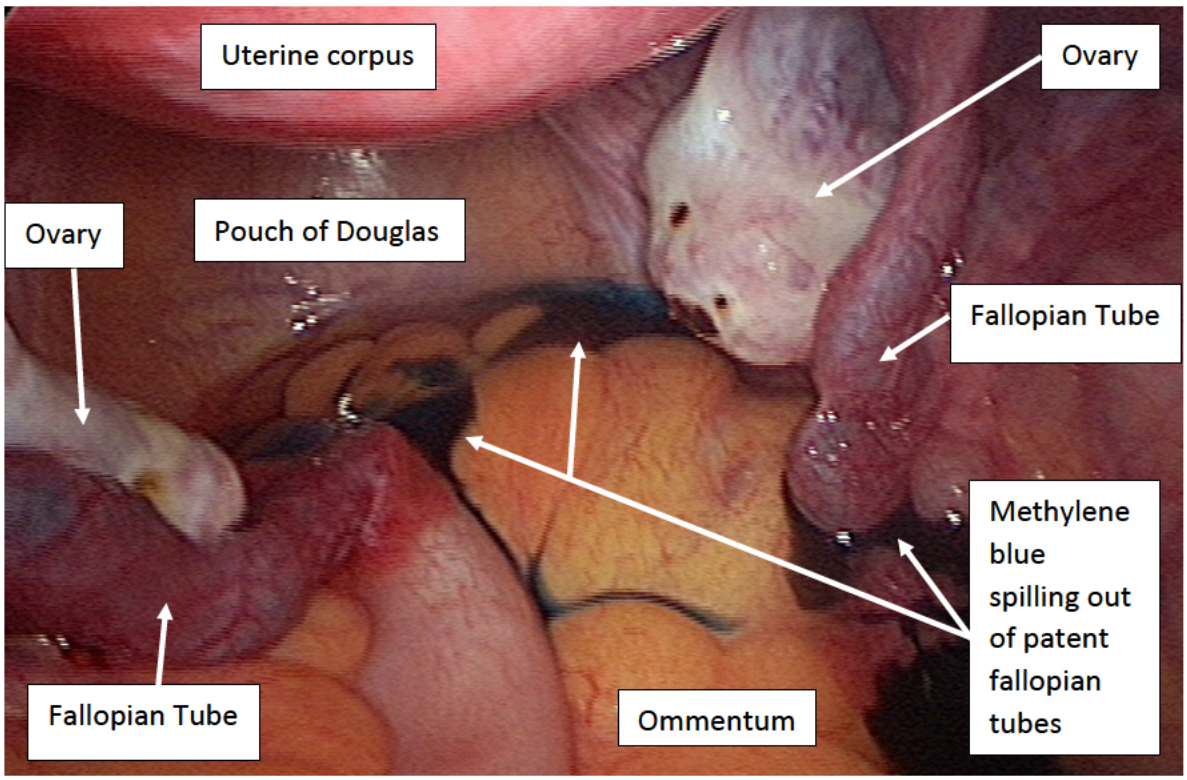


Figure 5: A still image picture from a laparoscopy and dye test from (109). *The methylene blue which has been introduced into the uterus from the vagina via the cervix can be seen accumulating in the Pouch of Douglas in the centre of the image.*

Laparoscopy and dye testing allows the direct visualisation of the tubes and remains the gold standard in establishing tubal patency (110). HSG and laparoscopy and dye testing of tubes

have been compared. In a subgroup analysis from a systematic review and meta-analysis comparing the methods (111), HSG had a sensitivity of 0.65 (95% CI 0.50 to 0.78) and specificity of 0.83 (95% CI 0.77 to 0.88). Therefore, NICE advocates for the use of HSG as a screening test for tubal patency in those without suspected pelvic pathology (96). HSG and HyCoSy have also been compared using laparoscopy and dye testing as the reference standard and randomised evidence shows comparable and concordant results between the two methods (112).

It should be noted that HyCoSy does not have the ionising radiation and associated risks of HSG, and also lacks the risks of intra-abdominal surgery and general anaesthetic of a laparoscopy and dye test. There is also the associated theatre and staff costs of a surgical procedure with the NHS National schedule of reference costs estimating nearly £1500 for a minor laparoscopic surgical procedure on the upper genital tract where as a contrast Fluoroscopy Procedures with duration of less than 20 minutes is £129.36 and an ultrasound scan with duration of less than 20 minutes, with contrast is £45.97 (14).

This discussion over the relative merits of tubal patency must be caveated by the acknowledgement that tubal patency does not equal tubal function and that currently there is no established method of examining tubal function and therefore an assumption is currently made that patency broadly equates to function (113).

Summary

I have provided an overview of miscarriage in this thesis introduction covering the basic anatomy, key terminology, outlined why this is an important area of research as well as risk factors for miscarriage and the management of miscarriage. To research all the areas where evidence is lacking would be a lifetime's work and so for my doctoral study and this thesis, I have chosen to focus on answering the following specific questions.

vii) Aims and Objectives

This thesis aims to improve the care of women and couples who have suffered from a miscarriage by answering the following specific questions?

A. What is the association between hydrosalpinx and miscarriage?
B. What is the effect of treatment for hydrosalpinx on miscarriage?
C. What is the prevalence of blocked tubes and hydrosalpinx in the recurrent miscarriage population?
D. What is the prognosis of women with blocked tubes and hydrosalpinx who are trying for a pregnancy?
E. What is the best method of managing a miscarriage?
F. What is the current body of evidence surrounding the management of miscarriage?

viii) Summary of thesis

Table 2: Summary of thesis and structured questions for each chapter of this thesis

Chapter Number	Population	Intervention	Comparison	Outcome(s)	Research Design
A. What is the association between hydrosalpinx and miscarriage?					
2	Women with an established pregnancy and a concurrent hydrosalpinx	NA	Women with an established pregnancy and no concurrent hydrosalpinx	• Miscarriage • Biochemical pregnancy loss • Clinical pregnancy loss • Ectopic Pregnancy	Systematic review and meta-analysis of observational studies
B. What is the effect of treatment for hydrosalpinx on miscarriage?					
2	Women with an established pregnancy and a concurrent hydrosalpinx	Treatment for a hydrosalpinx	No treatment for hydrosalpinx	• Miscarriage • Biochemical pregnancy loss • Clinical pregnancy loss • Ectopic Pregnancy	Systematic review and meta-analysis of observational studies and randomised trials
C. What is the prevalence of blocked tubes or hydrosalpinx in the recurrent miscarriage population?					
3	Women with recurrent miscarriage	NA		• Presence of tubal blockage • Presence of hydrosalpinx • 7 secondary outcomes	Primary observational cohort study
D. What is the prognosis of women with blocked tubes or hydrosalpinx who are trying for a pregnancy?					
3	Women with recurrent miscarriage and concurrent blocked	NA	Women with recurrent miscarriage and no concurrent blocked	• Pregnancy • Miscarriage • Live birth • 4 secondary outcomes	Primary observational cohort study

	tubes or hydrosalpinx		tubes or hydrosalpinx		
E. What is the best method of managing a miscarriage?					
4	Women having treatment for a miscarriage	• Expectant/ Placebo • Dilatation and curettage • Suction aspiration • Suction aspiration with cervical preparation • Mifepristone + Misoprostol • Misoprostol		• Complete miscarriage • Composite outcome of death and serious complications • 16 secondary outcomes	Systematic review and network-meta-analysis of randomised trials
F. What is the current body of evidence surrounding the management of miscarriage?					
5	Pregnant women or women trying to become pregnant	Any clinical, behavioural or health system intervention	Any alternative intervention or no intervention including placebo	• Any miscarriage outcome • Any live birth outcome	Systematic overview review of systematic reviews of randomised trials

CHAPTER TWO:

HYDROSALPINX & MISCARRIAGE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Authors and contributions:

Dr Jayasish Ghosh developed the search strategy, performed the search, study selection, data extraction, quality assessment, meta-analysis and prepared this manuscript, tables and figures.

Dr Hoda Harb, co-developed the search strategy, performed the study selection and data extraction and is co-first author for the resulting peer-reviewed published paper.

Dr Firas Al-Rshoud helped develop the search strategy, acted as second reviewer for study selection and data extraction.

Dr Bala Karunkaran acted as a second reviewer for study selection and data extraction.

Mr Derek Yates advised on the search strategy.

Dr Ioannis D Gallos acted as a second reviewer for quality assessment, acted as the final decision maker over author disagreements, checked the data extraction, helped with the meta-analysis and provided comments on the manuscript.

Prof Arri Coomarasamy provided comments on the manuscript.

This work has been published with Reproductive Biomedicine Online;

Publication 1: Harb H[*], Ghosh J[*], Al-Rshoud F, Karunakaran B, Gallos ID, Coomarasamy A. **Hydrosalpinx and pregnancy loss: a systematic review and meta-analysis.** Reprod Biomed Online. 2019 Mar;38(3):427-441. Doi: 10.1016/j.rbmo.2018.12.020.

[*] These authors contributed equally to this work

Abstract

Research question:

Is there an association between hydrosalpinx and miscarriage or pregnancy loss and what effect does the treatment of hydrosalpinx have on miscarriage or pregnancy loss?

Design:

A systematic review and meta-analysis was performed in order to investigate the research question. A literature search was performed in the following databases: MEDLINE, Embase, the Cochrane Library and Web of Science.

Results:

A 74% relative increase, for the risk of pregnancy loss, was shown in a meta-analysis of 14 observational studies for women who had a hydrosalpinx versus women who did not (risk ratio (RR) = 1.74, 95% confidence interval (CI): 1.43, 2.12). A decrease in pregnancy loss of roughly half was shown in a meta-analysis of seven randomized trials and six observational studies, for women whose hydrosalpinx had been treated versus women with no treatment (RR = 0.46, 95% CI: 0.34, 0.63).

Conclusions:

This systematic review and meta-analysis suggests that the risk of pregnancy loss is increased in the presence of hydrosalpinx. Treatment of hydrosalpinx may reduce the risk of pregnancy loss. It should be noted, all women in these studies conceived through IVF apart from in one study. The evidence is therefore not as certain for women who conceive naturally. Further

research should consider whether routine screening for hydrosalpinx should be carried out in women with recurrent miscarriages.

Introduction

As described in the introductory chapter, the fallopian tubes are of significant importance in pregnancy as the ampulla of the fallopian tube is usually the site of fertilisation. Fallopian tubes are usually less than 1.2 centimetres in diameter and ten to 13 centimetres in length when healthy (86). Yet they are fragile and can easily be damaged by numerous pathologies. When a pathology damages the distal free end of the fallopian tube, which is loosely associated with the ovary, it can become occluded. The fallopian tube can become distended and filled with fluid which is called a hydrosalpinx (plural hydrosalpinges).

Hydrosalpinx is found in approximately ten to 13% of infertile women using ultrasound scans (114,115). However, the actual incidence maybe as high as 30%, when better methods of detection such as hysterosalpingogram (HSG) and laparoscopic or open surgery are employed (105,116–118). More recent studies also support the higher incidence of hydrosalpinges, with it seen in around 19% of women with primary infertility and 29% of women with secondary infertility when diagnosed by HSG (119). *C. Trachomatis* and *N. Gonorrhoea,* which are the two most common sexually transmitted diseases both in the U.K. and the world (87,90), are a common cause of pelvic infection which can be associated with damage to the fallopian tubes (93). Others causes of fallopian tube damage have been previously discussed in my introduction, include endometriosis, pelvic surgery and non-gynaecological pelvic infections (93). In vitro fertilization (IVF) was first performed in order to treat infertility caused by tubal occlusion (120).

Hydrosalpinx is well known to reduce the chances of successful IVF. Hydrosalpinx is known to cause reduced implantation rates and subsequently reduced pregnancy rates (105,115) during IVF. Live-birth rates have been shown to be reduced by approximately half in women with hydrosalpinges (105,115). The reason for this has not been established, however, there are theories over the mechanism by which hydrosalpinx causes this negative effect. These include the theory of toxic effect of the hydrosalpinx fluid on embryo development (121). This theory is based mainly around the negative affects seen on mouse embryo culture of increasing concentrations of hydrosalpinx fluid (101). However, these results were not replicated in human models (103). The theory of impaired implantation ability and reduced endometrial receptivity (121). This theory suggests that hydrosalpinx fluid produces a chronic alteration of the intrauterine environment and the endometrium (102). Finally, the theory of mechanical hindrance (121). This theory suggests that due to the distal occlusion present, the hydrosalpinx fluid refluxes back into the uterus and produces a washout effect on the embryo which is implanting (98). It is unclear whether the peristaltic motion of the tube, ushers fluid towards the uterine cavity as it would an oocyte or whether there is flow out of the fimbrial end into the peritoneal cavity. Or that, due to the presence of a fluid interface caused by the hydrosalpinx fluid, there is mechanical impedance to implantation (99) due to surface tension. None of the proposed mechanisms for the adverse impact of hydrosalpinges on pregnancy are universally accepted and for some, the evidence is conflicting. In my opinion all the proposed mechanisms have some merit and logic behind them. It is likely that the negative impact of damaged fallopian tubes on implantation is likely to be multi-factorial with a combination of altered flow of oocytes through the tube, altered endometrial receptivity and immunological process as well as direct toxicity and mechanical impedance whether through

surface tension or a flushing effect. The aetiology of the damage to the fallopian tubes will likely influence which of the above proposed mechanisms has the most significant impact in individual cases.

It has subsequently been shown that clinical pregnancy and live birth rates are significantly improved by treatment of a hydrosalpinx during IVF (122). This is why NICE, since 2004, has recommended salpingectomy prior to IVF(96). It is worth noting that the majority of this published work is now over a decade old. It would appear that since a viable solution to bypass hydrosalpinges and non-functional fallopian tubes, has been found in IVF, researchers no longer see establishing the mechanism of negative impact as a priority.

It remains uncertain if a hydrosalpinx continues to pose a risk to the pregnancy of a women who has already achieved implantation. Additionally, it is not known if treatment of a hydrosalpinx could negate this increased risk if it exists. Therefore, this systematic review and meta-analysis investigates the effect of hydrosalpinx on pregnancy loss rates and whether treatment of a hydrosalpinx effects the pregnancy loss rates.

Materials and methods

Study selection

We examined women with a hydrosalpinx who conceived either spontaneously or via assisted conception including IVF. We compared this population to our control group of women who also conceived either spontaneously or via assisted conception including IVF but did not have

a hydrosalpinx or had had surgical treatment for a hydrosalpinx. The outcomes of interest for this review were pregnancy loss, biochemical pregnancy loss, clinical pregnancy loss and ectopic pregnancy. We searched: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science (inception - July 2017). The following key words and medical subject headings (MeSH) terms were used to create a search strategy: hydrosalpinx, hydrosalpinges, miscarriage, spontaneous fetal loss, spontaneous foetal loss, abortion, salpingectomy, salpingostomy, ultrasound-guided aspiration. In order to identify articles that were not captured by the above electronic search, the references of all included articles were manually examined. There were no limitations placed in any of the searches in terms of language or date. A data scientist assisted in formulating and carrying out the literature search.

There was a two-step process for study selection. Firstly, titles and abstracts were examined independently by two authors. After obtaining the full texts of the remaining references, a further round of study selection was performed by two authors independently. Any disagreements were resolved by discussion between the two authors or involvement of a third author. Studies were excluded if the population did not have hydrosalpinx or an outcome of interest was not reported. A previous history of pregnancy loss was not considered during study selection. The most current version of the paper was used, where duplicates were found. A core outcome set was not used when performing this review as one was not in existence.

Validity assessment

Methodological quality assessment was performed on all references that were selected for this review. The Newcastle-Ottawa scale (NOS) was used for non-randomised observational cohort studies (123). NOS assesses the selection of the study groups, the comparability of the study groups and the method of outcome assessment, and length and adequacy of follow-up to assess the overall risk of bias. The Cochrane risk of bias tool (RoB-2) was used for randomised trials (124). RoB-2 assesses the domains of random sequence generation and allocation concealment for selection bias, blinding of participants, personnel and outcome assessors for performed and detection bias, completeness of outcome data for attrition bias, selective reporting for reporting bias and any other bias within the studies in order to assess the overall risk of bias.

Statistical analysis

Review manager (RevMan 5.3) was used to perform all meta-analyses. Pregnancy loss rates were calculated and analysed per total number of pregnancies. Sub-group analyses for age under 35 and parity, as these are known confounders, were planned, Assessment of heterogeneity was via the chi-squared test. It should be noted that due to computational problems which occur when zero events are observed in one or both arms in an individual study, the Review Manager software used, corrects for this by adding a fixed value of 0.5 when calculating summary statistics (125).

Patient and Public Involvement

There was no involvement of patients or the public in this systematic review and meta-analysis.

Results

Literature search

Electronic and manual searches generated 2,680 references. The first round of study selection based solely on title and abstract excluded 2,571 publications. Full texts were obtained for the remaining 109 references. A further 86 publications did not satisfy the inclusion criteria of this review or were duplicates and so were excluded by the second round of study selection. A final number of 23 studies were included in this review (Figure 6).

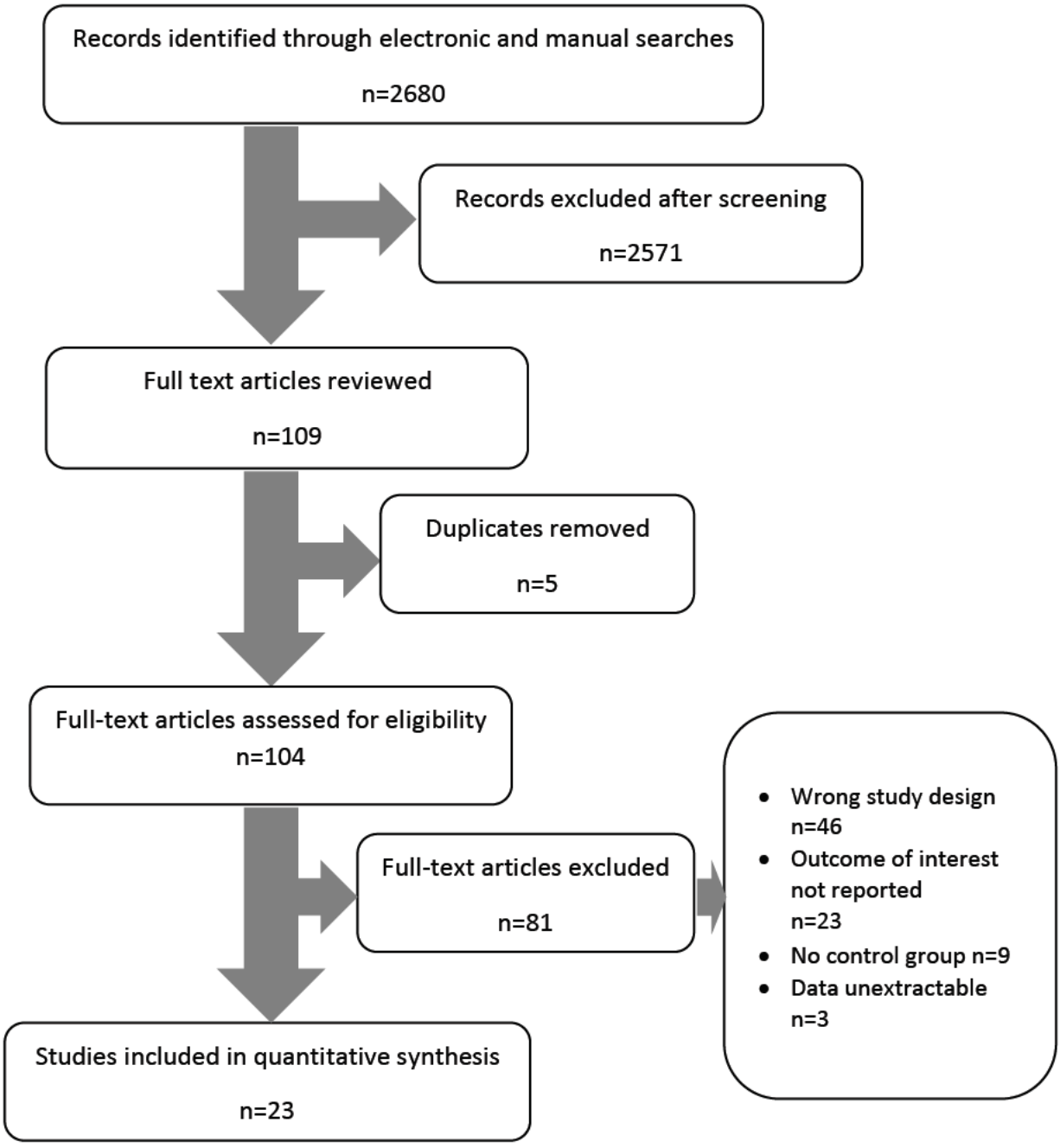


Figure 6: Study selection process for the systematic review of hydrosalpinx and pregnancy loss

Study characteristics

The full characteristics of all included studies are presented in tables three and four. There were 22 studies looking at the assisted conception or IVF population. One study looked at the

natural conception population (126). There were 14 observational studies which reported the outcome of pregnancy loss for women who had a hydrosalpinx when compared to women who did not have a hydrosalpinx. For 12 out of 14 of these observational studies, the control group was women with tubal disease with no evidence of hydrosalpinx. In one out of 14 observational studies, the control group was women with either tubal disease or unexplained infertility. In another one out of 14 observational studies, the control group was women who had had donor-egg IVF. For all studies, it was stated that semen analysis of their partners was acceptable for IVF or normal. We therefore felt that male factor infertility was controlled for in the individual studies themselves and does not impact our meta-analysis

The control group for all of the randomised controlled trials (RCT) looking at treatment for hydrosalpinx, was women with tubal factor infertility. To reduce the impact of age acting as a confounder for the results, all the studies had an age restriction of below 39 or 40 years. A total of 652 women with hydrosalpinx, with a mean age of 32.6 years (range 31 – 35) from 14 observational studies formed the experimental group for the main meta-analysis of pregnancy loss in women with versus without a hydrosalpinx. A total of 3669 women with no evidence of a hydrosalpinx, with a mean age of 33.4 years (range 29.7 – 34.4) formed the control group for this meta-analysis.

A total of 346 women who had their hydrosalpinx treated by any method, with a mean age of 30.3 years (range 28.2 – 33.4), from seven RCTs formed a subgroup based on study design, of the experimental group, for the second meta-analysis of pregnancy loss in women with a

treated hydrosalpinx versus women with an untreated hydrosalpinx. A total of 241 women with hydrosalpinx, with a mean age of 31.9 years (range 29.4 – 34) from these seven RCTs formed the control group for this subgroup in this second meta-analysis. The other subgroup based on study design in this second meta-analysis was formed by women from six observational studies. A total of 263 women who had their hydrosalpinx treated by any method, with a mean age of 32.9 years (range 30 – 35.5), formed the experimental group for this subgroup of the second meta-analysis. A further 231 women, with untreated hydrosalpinx, with a mean age of 32.9 years (range 31 – 34.5) formed the control group for this subgroup of the second meta-analysis.

Two studies reported BMI (127,128) . The number of previous miscarriages was reported in one study (126). How hydrosalpinges were defined and how they were diagnosed, varied amongst the studies. Barmat 1994 (129) defined a hydrosalpinx as a "tubular-shaped anechoic structure separate from the ovary" and diagnosed them on an USS that was performed to establish a baseline prior to controlled ovarian stimulation (COH) during an IVF cycle. Whereas Blazar 1999 (116) defined a hydrosalpinx as where "one or both tubes were enlarged and occluded distally" and where the diagnosis had been "demonstrated by hysterosalpingography and/or operative description". Zhou 2016 (127) used a more specific definition of a hydrosalpinx based on method of diagnosis. For a hydrosalpinx seen on an HSG, a definition of "obstructed Fallopian tubal umbrellas, expanded Fallopian tube ampullae, and accumulated contrast agent in the Fallopian tube, no contrast agent in the pelvic cavity" was used (127). And for a hydrosalpinx diagnosed on USS a definition of "streak-like or distorted

cystic mass found in unilateral or bilateral adnexa, with uneven thickness of cyst wall, incompletely separated by light bands, no colour blood flow signals in the cystic mass" was used (127).

Other differences were also noted regarding the gestation of a pregnancy up to which women were followed up. For example, Cohen 1999 (102) only followed women until their 12th week of gestation. However, Kassabji 1994 (130) followed up women into the second trimester up until their pregnancies were 20 weeks of gestation. Fleming 1996 (131) followed women up for longer and reported live birth rates. The definition the studies used in terms of pregnancy outcomes also varied. The majority used a gestational sac seen on an USS. However, Katz 1997 (114) also accepted documented trophoblastic tissue in pathology specimens after a pregnancy loss. Whereas, Murray 1998 (132) required the presence of a rising hCG (human chorionic gonadotrophin) titre prior to a gestational sac being seen on USS. Biochemical pregnancy loss was given as a separate outcome to clinical pregnancy loss in six of the observational studies (Figures nine and ten). The other studies only stated clinical pregnancy loss. There can be little clinical heterogeneity with the treatment of surgical salpingectomy, however, this is not the case with the tubal conservational techniques. Adequate description of these tubal conservational techniques was not present.

Table 3: Full study characteristics of all observational cohort studies looking at pregnancy loss in women with hydrosalpinx compared to women without hydrosalpinx

Study	Study Design	Participants	Comparator	Outcomes reported
Akman, 1996 (133)	Retrospective observational cohort	10 women (mean age 31.9) undergoing 14 In-Vitro Fertilisation (IVF) cycles with known tubal disease and evidence of a hydrosalpinx diagnosed by ultrasound scan (USS) and confirmed on hystero-salpingogram (HSG) or laparoscopy between 1st Sept 1993 – 1st Nov 1995, at The Women's Hospital fertility centre at the Greater Baltimore Medical Centre, MD, USA.	74 patients (mean age 34) undergoing 98 IVF cycles with known tubal disease but no evidence of a hydrosalpinx on USS during the same time period.	Clinical pregnancy (defined as presence of a gestational sac on USS or presence of trophoblastic tissue in pathology specimens; pregnancy loss was defined as births before 20 weeks of gestation), ectopic pregnancy and biochemical Pregnancy loss.
Andersen, 1994 (115)	Observational cohort	62 patients (mean age 32.7) undergoing 104 IVF cycles with tubal infertility, who had uni/bilateral hydrosalpinges detected by transvaginal ultrasound scan (TV USS), between May 1991 – May 1993, at the Mermaid Clinic and Herlev Hospital, Denmark.	671 patients (mean age 33.5) who underwent IVF with tubal infertility or unexplained infertility or infertility due to other factors and with no hydrosalpinges detected by TV USS treated during the same time period.	Live births, clinical pregnancy, clinical pregnancy loss, ectopic pregnancy. Biochemical pregnancy was defined as a positive serum human chorionic gonadotrophin and was reported.
Barmat, 1999 (129)	Retrospective observational cohort	60 patients under the age of 40 (mean age 35.0) with tubal factor infertility and uni/bilateral hydrosalpinges on baseline TV USS undergoing IVF between Jan 1989 and Dec 1995, at The Centre for Reproductive Medicine and Infertility, Cornell Medical Centre.	940 patients under the age of 40 (mean age 34.0) with tubal factor infertility but no hydrosalpinx on baseline TV USS undergoing treated during the same time period.	Live births, clinical pregnancy (defined as the presence of a gestational sac and fetal heartbeat visualised on USS), c clinical pregnancy loss (defined as a pregnancy loss before 20 weeks of gestation), ectopic pregnancy and biochemical pregnancy (defined as a B-hCG level >5mIU/ml 10 days post embryo transfer on 2 separate occasions without evidence of fetal heart activity or a gestational sac).
Blazar, 1997 (116)	Retrospective observational cohort	67 patients (mean age 33.7) undergoing 155 IVF cycles with tubal disease infertility and persistent hydrosalpinx, demonstrated by HSG, or USS and/or operative description, from May 1988 to Oct 1994, at Dept. of O&G, Women and Infants Hospital, Brown University School of Medicine, Rhode Island.	183 patients (mean age 33.8) undergoing 359 IVF cycles with tubal disease infertility without hydrosalpinx confirmed by HSG or at laparoscopy treated during the same time period.	Clinical pregnancy (defined as sonographic documentation of an intrauterine pregnancy), clinical pregnancy loss (defined as the spontaneous loss of a clinical pregnancy), ectopic pregnancy and biochemical pregnancy.

Cohen, 1999 (102)	Retrospective observational cohort	10 patients (mean age not stated) undergoing 13 cycles of IVF using donated oocytes with hydrosalpinges confirmed on TV USS or HSG, at the Division of Reproductive Endocrinology, Columbia Presbyterian Medical Centre, Columbia University, New York.	100 patients (mean age not stated) undergoing 108 cycles of IVF using donated oocytes without hydrosalpinges on TV USS or HSG.	Clinical pregnancy (defined by a documented fetal heart rate with an intrauterine pregnancy), clinical pregnancy loss, biochemical pregnancy (defined as a positive B-hCG) and ectopic pregnancy. Follow up was up until at least 12 weeks of gestation
Fleming, 1996 (131)	Retrospective observational cohort	79 patients (mean age 32.0) with tubal infertility and hydrosalpinges identified by laparoscopy or HSG undergoing their first cycle of IVF between July 1989 to June 1993, at the University of Bristol IVF Unit, BUPA Hospital Bristol, Bristol.	198 patients (mean age 33.0) with inflammatory tubal damage but no hydrosalpinges undergoing their first cycle of IVF at the same fertility centre and during the same time period.	Live birth, clinical pregnancy (defined as the demonstration of one or more gestational sacs by USS, 4 weeks after treatment), clinical pregnancy loss, ectopic pregnancy, and biochemical pregnancy loss.
Freeman, 1998 (134)	Retrospective observational cohort	35 patients aged between 24 – 39 (mean age 31.7) undergoing IVF with tubal factor infertility with hydrosalpinx diagnosed by HSG or laparoscopy/laparotomy, or on USS prior to IVF between Jan 1993 – June 1996, at the Centre for Assisted Reproduction and Reproductive Endocrinology, Nashville Fertility Centre.	219 patients aged between 24 – 39 (mean age 34.4) undergoing IVF with tubal factor infertility with no hydrosalpinx seen on USS or HSG or non-tubal factory infertility at the same fertility centre and during the same time period.	Live birth, clinical pregnancy (defined as USS visualization of an intrauterine gestational sac), clinical pregnancy loss, biochemical pregnancy and ectopic pregnancy
Katz, 1996 (114)	Retrospective observational cohort	79 patients < 40 years of age undergoing (mean age 31.9) 118 IVF cycles with tubal disease infertility, who had a hydrosalpinx seen on USS during or prior to IVF between 12th Oct 1987 and 31st March 1995, at The Women's Hospital Fertility Centre, Baltimore, Maryland.	812 patients < 40 years of age (mean age 33.5) undergoing 1,648 IVF cycles with tubal disease infertility who did not have a hydrosalpinx seen on USS during or prior to IVF at the same fertility centre.	Live birth, clinical pregnancy (defined as the presence of a gestational sac on USS or by documenting trophoblastic tissue in pathology specimens from abortions), clinical pregnancy loss (defined as a birth before 20 weeks of gestation), ectopic and biochemical pregnancy.
Murray, 1998 (132)	Retrospective observational cohort	26 patients undergoing 47 cycles of IVF < 40 years of age (mean age 31.5) with tubal factor infertility and a hydrosalpinx seen on HSG and/or surgical assessment between Nov 1991 and Jan 1996, at The Shady Grove Fertility Centre, Rockville, Maryland.	97 patients undergoing 148 cycles of IVF < 40 years of age (mean age 33.8) with tubal factor infertility with no hydrosalpinges seen on HSG and/or surgical assessment at the same fertility centre and during the same time period.	Clinical pregnancy (defined as an intrauterine gestational sac identified by TV USS after a rising hCG titre), clinical pregnancy loss, ectopic pregnancy, biochemical pregnancy.
Ng, 1997 (135)	Retrospective observational cohort	43 patients, less than 38 years old (mean age 32.0) with tubal factor infertility and with hydrosalpinx, on laparoscopy/ laparotomy on HSG undergoing their first cycle of IVF from 1st Jan 1993 – 31st Dec 1995, at the Assisted Reproduction Unit at the Dept. of O&G, Queen Mary Hospital, Hong Kong.	101 patients, less than 38 years old (mean age 33.0) with tubal factor infertility with no hydrosalpinx confirmed on either laparoscopy or laparotomy or HSG undergoing their first cycle of IVF at the same fertility centre and during the same time period.	Live birth, Clinical pregnancy (defined as the presence of one or more intrauterine gestation sacs on USS or the demonstration of gestational product in the uterine evacuate), clinical pregnancy loss and ectopic pregnancy.

Sharara, 1996 (136)	Prospective observational cohort	63 patients aged less than 40 years of age (mean age 33.7) undergoing 103 cycles of IVF with tubal factor infertility with a hydrosalpinx diagnosed prior to IVF via HSG and/or laparoscopy between Jan 1990 and Dec 1994, at the Division of Reproductive Endocrinology and Infertility, Michael Reese Hospital and Fertility Centre, Illinois, and the Division of Reproductive Endocrinology and Infertility, Saint Barnabas Medical Centre, New Jersey, USA.	60 patients aged less than 40 (mean age 34.1) undergoing 89 cycles of IVF with tubal factor infertility with no hydrosalpinx seen prior to IVF via HSG and/or laparoscopy at the same fertility centre and during the same time period.	Pregnancy and ectopic pregnancy were reported but not defined. Pregnancy loss was defined as a 1st trimester miscarriage and was reported. Follow up was to 20 weeks of gestation.
Strandell, 1994 (105)	Retrospective observational cohort	81 patients (mean age not stated) undergoing 227 IVF cycles with uni/bilateral hydrosalpinx diagnosed by HSG and laparoscopy or laparotomy between Jan 1990 to June 1993, at the Sahlgrenska University Hospital, Goteborg, Sweden.	173 patients (mean age not stated) undergoing 367 IVF cycles with tubal lesions without distal occlusion i.e. no hydrosalpinges of either of the tubes, diagnosed by HSG and laparoscopy or laparotomy at the same fertility centre and during the same time period.	Clinical pregnancy (defined as an embryo diagnosed by TV USS and was reported), and clinical pregnancy loss . Follow up was to 22 weeks of gestation
Vandromme, 1995 (137)	Retrospective observational cohort	37 patients undergoing 69 IVF cycles, less than 40 years of age (mean age 33.7), who had a uni/bilateral hydrosalpinx at HSG or laparoscopy, between March 1989 – June 1993, at The IVF clinic, Free University Brussels, Saint-Pierre Hospital, Brussels, Belgium.	41 patients undergoing 67 IVF cycles, less than 40 years of age (mean age 34.3), who had tubal damage from sterilisation or antecedents of bilateral salpingectomy but no hydrosalpinges at the same fertility centre and during the same time period.	Clinical pregnancy (defined as the associated progressive rise in B-hCG to >500mIU/ml with the appearance of a gestational sac at USS), clinical pregnancy loss (defined as the loss of a clinical pregnancy before 20 weeks of gestation). Follow up was to 20 weeks of gestation
Zhou, 2016 (127)	Retrospective observational cohort	35 cycles of IVF in patients aged up to 37 years (mean age 31.0) with a BMI of less than 25 with tubal infertility and on HSG or USS between March 2011 and July 2015, at the Reproductive Medical Centre, 105 Hospital of People's Liberation Army, Anhui, China.	441 cycles of IVF in patients aged up to 37 years (mean age 29.7) with a BMI of less than 25 with tubal infertility who had no hydrosalpinges on HSG or USS at the same fertility centre and during the same time period.	Clinical pregnancy (defined as observation of a gestational sac on day 30-35 after embryo transfer) , clinical pregnancy loss (defined as embryo developmental arrest or spontaneous abortion at <12 weeks of gestation) and ectopic pregnancy

Table 4: Full study characteristics of all observational cohort studies and randomised controlled trials looking at pregnancy loss in women with untreated hydrosalpinx compared to women with treated hydrosalpinx

Study	Study Design	Participants	Comparator	Outcomes reported
Freeman, 1998 (134)	Retrospective observational cohort	35 women, aged between 24 – 39 (mean age 33.6), undergoing IVF with tubal factor infertility with hydrosalpinx diagnosed by HSG, USS or on a laparoscopy/laparotomy between Jan 1993 – June 1996, at the Centre for Assisted Reproduction and Reproductive Endocrinology, Nashville, Texas.	32 women aged between 24 – 39 (mean age 31.7) undergoing IVF with tubal factor infertility and treatment of hydrosalpinges prior to IVF via salpingectomy or neosalpingostomy with subsequent absence of hydrosalpinges confirmed by HSG at the same fertility centre and during the same time period.	Clinical pregnancy (defined as USS visualization of an intrauterine gestational sac), clinical pregnancy loss, biochemical pregnancy and ectopic pregnancy. Follow up was to live birth.
Kassabji, 1994 (130)	Retrospective observational cohort	118 women (mean age 34.5) undergoing 283 IVF cycles with uni or bilateral hydrosalpinx confirmed with HSG or laparoscopy undergoing IVF between 1988 and 1992, at The Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Virginia.	157 women (mean age 35.5) undergoing 272 IVF cycles with bilateral salpingectomy >6 months before start of IVF cycle at the same fertility centre and during the same time period.	Clinical pregnancy (defined as a pregnancy detected by 1st trimester USS), clinical pregnancy loss (defined as a pregnancy loss prior to 20 weeks of gestation) and ectopic pregnancy. Follow up was to 20 weeks of gestation
Murray, 1998 (132)	Retrospective observational cohort	26 women aged < 40 years (mean age 31.5) undergoing 47 cycles of IVF with tubal factor infertility and a hydrosalpinx seen on HSG or surgical assessment between Nov 1991 and Jan 1996, at The Shady Grove Fertility Centre, Rockville, Maryland.	37 women aged < 40 years (mean age 33.1) undergoing 45 cycles of IVF with tubal factor infertility who had surgical correction of previous hydrosalpinges via neosalpingostomy, salpingectomy or proximal tubal occlusion at the same fertility centre and during the same time period.	Clinical pregnancy (defined as an intrauterine gestational sac identified by TV USS after a rising hCG titre), clinical pregnancy loss and ectopic pregnancy.
Shelton, 1996 (138)	Prospective observational cohort	15 women (mean age 33.7) undergoing 52 cycles of IVF with uni/bilateral hydrosalpinges as detected by HSG at The Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Norfolk, VA.	The same 15 women (mean subsequent age not stated) undergoing 22 cycles of IVF with uni/bilateral hydrosalpinges after having laparoscopic uni/bilateral salpingectomy for treatment of hydrosalpinges between July 1993 and July 1994 at the same institution.	Clinical pregnancy (defined as a pregnancy detected by first trimester) and clinical pregnancy loss. Follow up was to at least 20 weeks.
Vandromme, 1995 (137)	Retrospective observational cohort	37 women aged less than 40 years (mean age 33.7) undergoing 69 IVF cycles, who had a uni/bilateral hydrosalpinx on HSG or at laparoscopy between March 1989 – June 1993, at the IVF clinic, Free	22 women, less than 40 years of age (mean age 34.3), undergoing 42 IVF cycles who had bilateral salpingectomy or salpingoplasty for treatment of	Clinical pregnancy (defined as the associated of a progressive rise in B-hCG to >500mIU/ml with the appearance of a gestational sac at USS), clinical pregnancy loss (defined as the loss of a clinical

		University Brussels, Saint-Pierre Hospital, Brussels, Belgium.	hydrosalpinges at the same fertility centre and during the same time period.	pregnancy before 20 weeks of gestation) and ectopic pregnancy. Follow up was to 20 weeks of gestation.
Zhou, 2016 (127)	Observational retrospective cohort	35 cycles of IVF in women aged 37 or under (mean age 31.0) with a BMI of less than 25 with tubal infertility and unilateral or bilateral hydrosalpinges on HSG or USS between March 2011 and July 2015, at the Reproductive Medical Centre, 105 Hospital of People's Liberation Army, Anhui, China.	122 cycles of IVF in women aged 37 or under (mean age 30.0) with a BMI of less than 25 with tubal infertility and who had their hydrosalpinges drained via USS guided aspiration at the same fertility centre and during the same time period.	Clinical pregnancy (defined as observation of a gestational sac on day 30-35 after embryo transfer and was reported), clinical pregnancy loss was defined as embryo developmental arrest or spontaneous abortion at <12 weeks of gestation and was reported and ectopic pregnancy. Follow up was to 20 weeks of gestation.
Dechaud, 1998 (139)	Randomised control trial	30 women less than 40 years of age (mean age 30.6) undergoing 49 IVF cycles with severe tubal factor infertility and either hydrosalpinx or salpingitis isthmica nodosa on HSG or presence of proximal nodes or an inflammatory and thick walled hydrosalpinx at laparoscopy between April 1992 and June 1996, at the Centre Hospitalier Universitaire Arnaud de Villeneuve, Montpellier, France.	30 women less than 40 years of age (mean age 31.7) undergoing 59 IVF cycles who had bilateral salpingectomy due to severe tubal pathology and non-functional tubes not suitable for surgical repair at the same fertility centre and during the same time period.	Pregnancy, pregnancy loss and ectopic pregnancy. Follow up was to live birth
Fouda, 2011 (128)	Randomised control trial	53 women undergoing IVF aged between 18 and 37 years of age (mean age 29.4) with a BMI between 19 and 29 with uni/bilateral hydrosalpinges visible by USS between Oct 2006 and May 2010, at the Assisted Conception Unit, Ahmed Elgazzar Hospital, Cairo, Egypt.	54 women undergoing IVF aged between 18 and 37 years of age (mean age 28.2) with a BMI between 19 and 29 who had uni or bilateral hydrosalpinges but had undergone USS guided aspiration of hydrosalpingeal fluid at the time of oocyte retrieval at the same fertility centre and during the same time period.	Clinical pregnancy (defined as the presence of an intrauterine gestational sac detected by TV USS), clinical pregnancy loss (defined as the termination of pregnancy before the 20th week of gestation) and ectopic pregnancy. Follow up was to 20 weeks
Goldstein, 1998 (140)	Randomised control trial	16 women aged between 22 and 38 years with hydrosalpinges undergoing IVF, at the Central Park West Fertility Centre, New York, New York, USA.	15 women undergoing IVF between 22 and 38 years of age who underwent selective salpingostomy-salpingectomy to treat hydrosalpinges prior to IVF during an unspecified time period at the same fertility centre.	Pregnancy, pregnancy loss, ectopic pregnancy. Follow up was to live birth.
Hammadieh, 2008 (141)	Randomised control trial	34 women undergoing IVF under the age of 40 (mean age 33.9) with uni/bilateral hydrosalpinges identified on USS between October 1999 and June 2003, at the Assisted Conception Unit of Birmingham Women's Hospital, Birmingham, UK	32 women undergoing IVF under the age of 40 (mean age 33.4) who underwent USS guided aspiration of their uni/bilateral hydrosalpinges as identified on USS at the same fertility centre and during the same time period.	Clinical pregnancy (defined as the presence of a gestational sac on TV USS), clinical pregnancy loss (defined as any pregnancy loss before 12 weeks of gestation), ectopic pregnancy, and biochemical pregnancy (defined as a positive urinary hCG 14 days after embryo transfer). Follow up was to 12 weeks of gestation.

Kontoravdis, 2006 (142)	Randomised control trial	14 women undergoing their 1st cycle of IVF, aged 41 or under (mean age 34.0) with a uni/bilateral hydrosalpinx confirmed on HSG, between 2000 and June 2005, at the Second Dept. of O&G, University of Athens, Aretaieion Hospital Greece or the Centre for Human Reproduction, Genesis Clinic, Athens, Greece.	92 women undergoing their 1st cycle of IVF, aged 41 or under (mean age 30.4) who had previously undergone either laparoscopic uni/bilateral proximal tubal occlusion or laparoscopic uni/bilateral salpingectomy to treat hydrosalpinges >2 completed menstrual cycles prior to their IVF at the same fertility centre and during the same time period.	Clinical pregnancy (defined as gestational sac +/- fetal pole confirmed by USS 4 weeks after embryo transfer), clinical pregnancy loss, and ectopic pregnancy.
Strandell, 1999 (122)	Randomised control trial	88 women undergoing IVF less than 39 years of age (mean age 31.8) with a hydrosalpinx confirmed on HSG or laparoscopy, between Jan 1994 to May 1998, from 9 Nordic IVF centres across Sweden, Denmark, Norway and Iceland.	116 women undergoing IVF less than 39 years of age (mean age 31.8) who had had either laparoscopic uni/bilateral salpingectomy or proximal ligation and distal fenestration to treat hydrosalpinx greater than 2 months prior to IVF at the same fertility centres and during the same time period.	Clinical pregnancy (defined as gestational sac verified by USS), clinical pregnancy loss and ectopic pregnancy. Follow up was to live birth.
Zolghadri, 2006 (126)	Randomised control trial	6 women aged less than 40 with recurrent (>3) miscarriage and unilateral hydrosalpinx as defined by occlusions and fluid filled areas in the tubes, detected by USS and HSG in whom other causes of miscarriage were excluded, from March 2002 to Sept 2004, at Dept. of O&G, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.	7 women aged less than 40 with recurrent (>3) miscarriage and unilateral hydrosalpinx detected by USS and HSG in whom other causes of miscarriage were excluded, and with the same characteristics, who underwent laparoscopic proximal tubal fulguration using electrocautery and tubal division at the same fertility centre and during the same time period.	Clinical pregnancy (defined as an intrauterine pregnancy), clinical pregnancy loss and ectopic pregnancies. Also reported was the range of the number of previous miscarriages. Follow up was to live birth.

Validity assessment

The full methodological quality assessment of all included studies using the NOS and RoB-2 tools for observational and randomised studies respectively, is presented in tables five and six. There was a variable risk of bias across the included studies. Two observational studies were awarded the maximum nine stars with three given eight stars denoting high quality methodological practices according to the NOS tool. However, four stars were awarded to four studies and five stars were awarded to a further four studies denoting a higher risk of bias and poorer methodologies. The remaining three were awarded either seven or six stars on the NOS. Using the RoB-2 tool, the seven randomised studies were also judged to be on variable risk of bias. Only two were conducted in a manner as to be judged at low risk of bias. Two were judged to be at high risk of bias due to poor methodological conduct with the remaining three were felt to warrant some concerns over a potential risk of bias.

Table 5: Quality assessment of non-randomised cohort studies using the Newcastle-Ottawa Scale for cohort studies

	Selection				Comparability	Outcome			Comments
Study Author, Year of Publication	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of the exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total rating
Akman, 1996	✸	✸	✸	✸	Not controlled for any confounders	No description of ongoing pregnancy outcome	Up to 20 weeks of gestation	✸	5 ✸
Anderson, 1994	✸	✸	✸	✸	Not controlled for any confounders	No description of ongoing pregnancy outcome	Up to 2nd trimester	✸	5 ✸
Barmat, 1999	✸	✸	✸	✸	Not controlled for any confounders	No description of ongoing pregnancy outcome	Up to 20 weeks of gestation	✸	5 ✸
Blazar, 1997	✸	✸	✸	✸	✸	No description of ongoing pregnancy outcome	Not specified	✸	6 ✸
Cohen, 1999	No description	No description	✸	✸	✸✸	No description of ongoing pregnancy outcome	Up to 12 weeks of gestation	Some pregnancies in non-hydrosalpinx group appear not to have been accounted for – no further details	4 ✸
Flemming, 1996	✸	✸	✸	✸	✸	✸	✸	✸	8 ✸
Freeman, 1998	✸	✸	✸	✸	Hydrosalpinx group were significantly	No description of ongoing	✸	✸	6 ✸

					younger but the study did not provide any adjusted estimates	pregnancy outcome				
Katz, 1996	★	★	★	★	★	★	★	★	8	★
Kassabji, 1994	★	★	★	★	★★	★	Up to 20 weeks of gestation	★	8	★
Murray, 1998	★	★	★	★	★★	★	★	★	9	★
Ng, 1997	★	★	★	★	★★	★	★	★	9	★
Sharara, 1996	★	★	Not clear if all patients underwent an HSG or Laparoscopy	★	★	No description of ongoing pregnancy outcome	Up to 20 weeks of gestation	★	5	★
Shelton, 1996	No description	★	★	★	★	★	Up to 20 weeks of gestation	★	6	★
Strandell, 1994	★	★	Not clearly described	★	Not controlled for any confounders	No description of ongoing pregnancy outcome for all women	Some women were followed up to 22 weeks but not clear how many	★	4	★
Vandromme, 1995	★	★	Not clear if all patients underwent a HSG or Laparoscopy	★	Not controlled for any confounders	No description of ongoing pregnancy outcome	Up to 20 weeks of gestation	★	4	★
Zhou, 2016	★	★	★	★	★★	No description of ongoing pregnancy outcome	Up to 20 weeks of gestation	★	7	★

Table 6: Quality assessment of randomised trials using the Cochrane risk of bias in randomised trials tool (RoB-2)

Author, Year of Publication	Risk of bias judgement arising from randomisation process	Risk of bias judgement due to deviations from intended interventions	Risk of bias judgement for bias due to missing outcome data	Risk of bias judgement in measurement of the outcome	Risk of bias judgement for bias in selection of the reported result	Overall risk of bias judgement
Dechaud, 1998	Some concerns – Randomisation process not mentioned	High – Women were randomised at the time of laparoscopy but there was no mention about deviations as the carers were aware of the allocation	Low	Low	Low	High
Fouda, 2011	Low	Low	Low	Low	Low	Low
Goldstein, 1998	Some concerns – Randomisation process not mentioned	Some concerns –It is not mentioned there were no deviations from the intended procedure	Low	Low	Some concerns – As just abstract obtained no information about multiple analyses	High
Hammadieh, 2008	Low	Low	Low	Low	Low	Low
Kontoravdis, 2006	Low	Some concerns – It was not mentioned there were no deviations from the intended procedure	Low	Low	Low	Some concerns
Strandell, 1999	Low	Some concerns – The groups were imbalanced	Low	Low	Low	Some concerns
Zolgadhri, 2006	Low	Some concerns – It was not mentioned there were no deviations from the intended procedure and minimal information was presented to assess for balance between groups	Low	Low	Low	Some concerns

Pregnancy loss in women with and without hydrosalpinx

Meta-analysis of results from the fourteen observational studies shows an increased pregnancy loss risk for women who had a hydrosalpinx versus women with no hydrosalpinx (RR 1.74, 95% CI: 1.43, 2.12) (Figure 7). No concerning statistical heterogeneity across the 14 observational studies was detected (I^2 = of 31%).

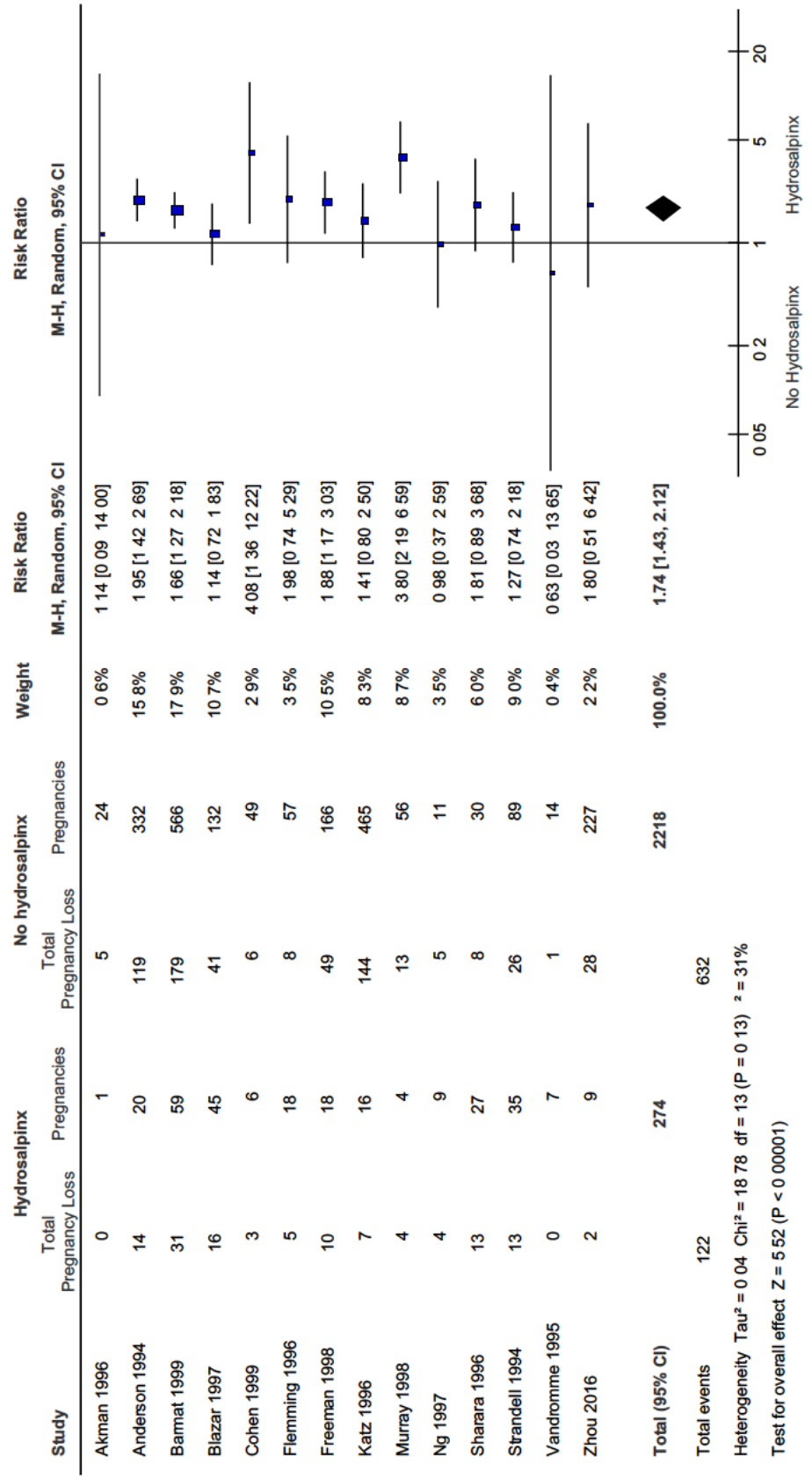


Figure 7: Meta-analysis of studies comparing pregnancy loss in women with hydrosalpinx to women with no hydrosalpinx

Pregnancy loss in women with and without treatment for hydrosalpinx

Meta-analysis of the risk ratios from the seven randomized studies shows an over 50% reduction for pregnancy loss risk in treated women (any intervention) versus untreated women (risk ratio (RR) = 0.49; 95% confidence interval (CI): 0.30–0.79) (Figure 8). Meta-analysis of the risk ratios from the six observational studies similarly found an over 50% reduction for pregnancy loss risk in treated women (any intervention) versus untreated women (RR 0.45; 95% CI 0.31–0.66) (Figure 8). Overall, no statistical heterogeneity was detected across both subgroups of studies (I^2 = 0%).

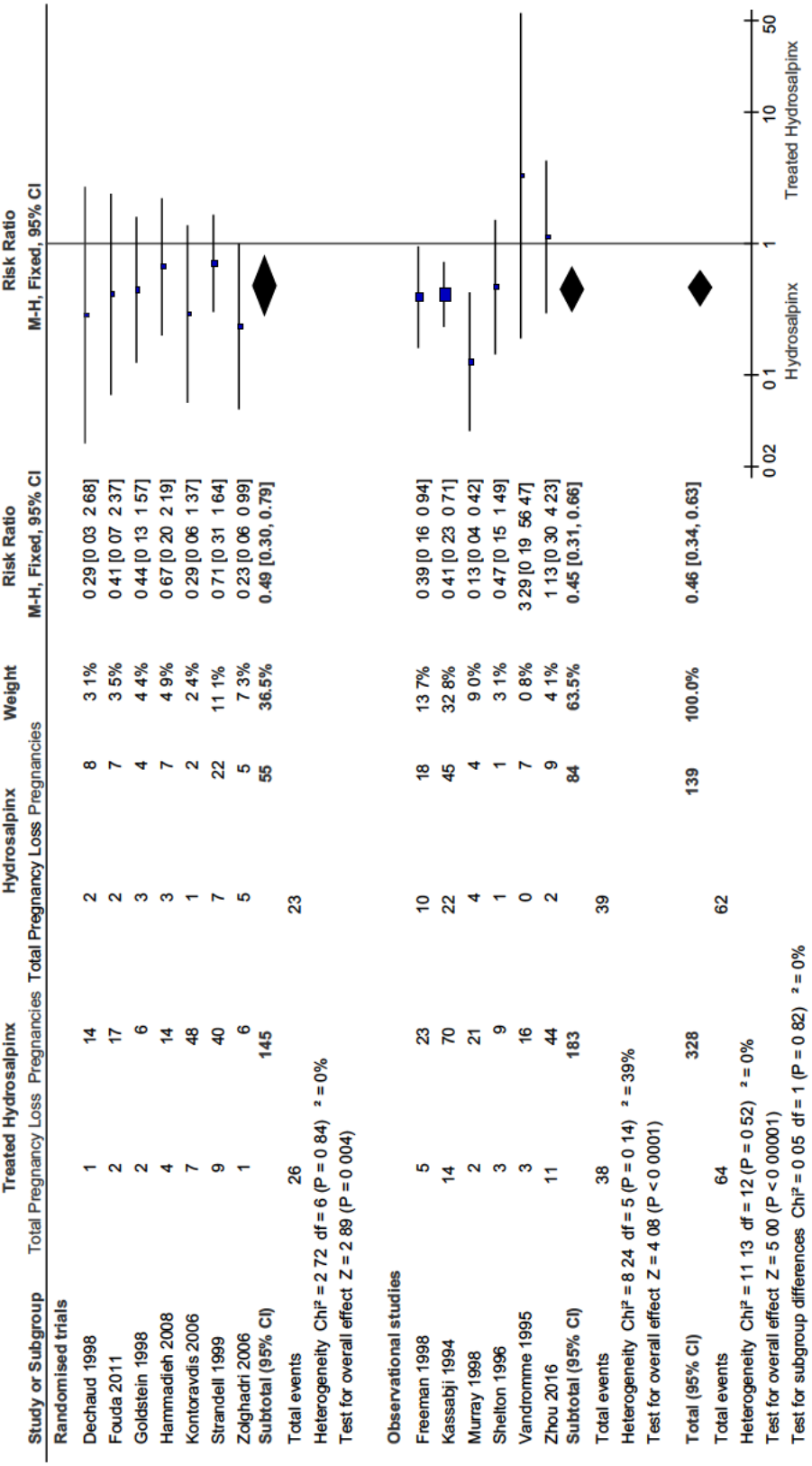


Figure 8: Meta-analysis of studies comparing pregnancy loss in women who had treatment (all interventions) for hydrosalpinx to women who did not undergo treatment for hydrosalpinx sub-grouped according to study type

Sub-group analysis of the different methods of treatment of a hydrosalpinx shows potential differences in the efficacy of the different methods of treatment in terms of reducing the risk of pregnancy loss. Ultrasound-guided drainage was used in three studies (two randomised and one observational) which compared pregnancy loss in women with a treated hydrosalpinx to women with no treatment for their hydrosalpinx. Meta-analysis of these three studies was inconclusive over whether ultrasound-guided drainage reduced the risk of miscarriage (RR 0.75; 95% CI 0.34–1.63) (Figure 9). However, the reduction in risk of pregnancy loss was much larger with the other two subgroups of treatment for hydrosalpinx. Seven studies (five randomised and two observational studies) used salpingectomy as a treatment for hydrosalpinx. Meta-analysis of this subgroup shows a larger reduction in the risk of pregnancy loss (RR 0.44; 95% CI 0.30–0.64) with no evidence of statistical heterogeneity (I^2 = 0%) (Figure 9). And three studies (all observational) used tubal conservational surgery to treat women with hydrosalpinx and compared them to women with untreated hydrosalpinx. Freeman 1998 (134) and Murray 1998 (132) performed neosalpingostomy whereas Vandromme 1995 (137) performed salpingoplasty. Meta-analysis of these three studies shows an even larger reduction in the risk of pregnancy loss in women who had their hydrosalpinx treated versus women with an untreated hydrosalpinx (RR 0.39; 95% CI 0.21–0.75) but there was severe statistical heterogeneity (I^2 = 64%) in this subgroup (Figure 9). It should be noted that some patients in this final subgroup, however, underwent salpingectomy. For this review, we assumed salpingectomy was only performed when more conservative surgery on the fallopian tube failed or was not possible, however, this was not explicitly stated in all of the three studies.

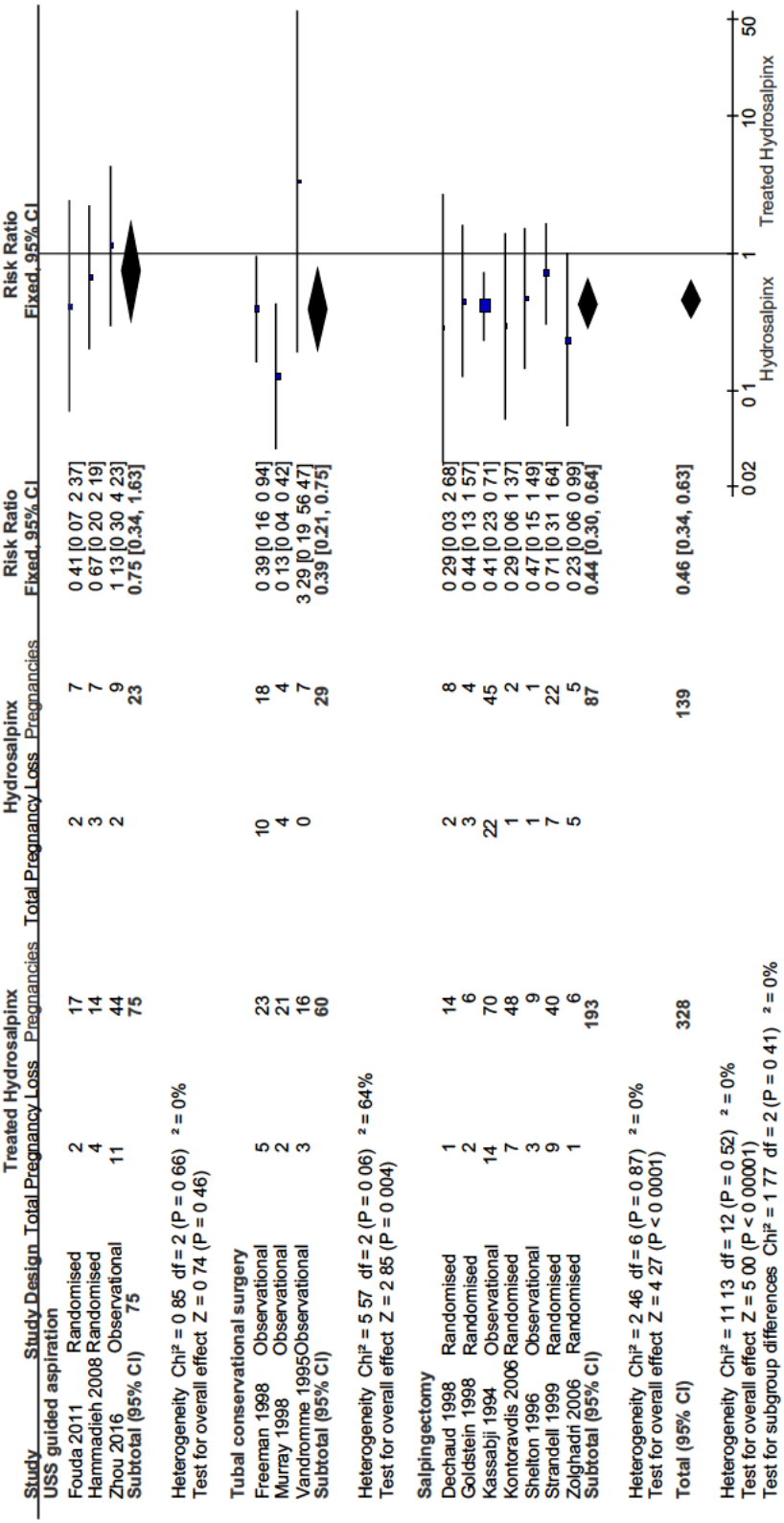


Figure 9: Meta-analysis of studies comparing pregnancy loss in women who had treatment (all interventions) for hydrosalpinx to women who did not undergo treatment for hydrosalpinx sub-grouped according to intervention type.

Biochemical pregnancy loss in women with and without hydrosalpinx

Biochemical pregnancy loss specifically was reported separate to clinical pregnancy loss in six of the observational studies, potentially allowing us to examine at what stage of a pregnancy's development a hydrosalpinx maybe most harmful. Meta-analysis of the risk ratios from these six studies shows that the risk of a biochemical pregnancy loss in women with a hydrosalpinx was more than doubled that of women with no hydrosalpinx (RR 2.36; 95% CI 1.55–3.59) with no severe statistical heterogeneity (I^2 = 43%) (Figure 10).

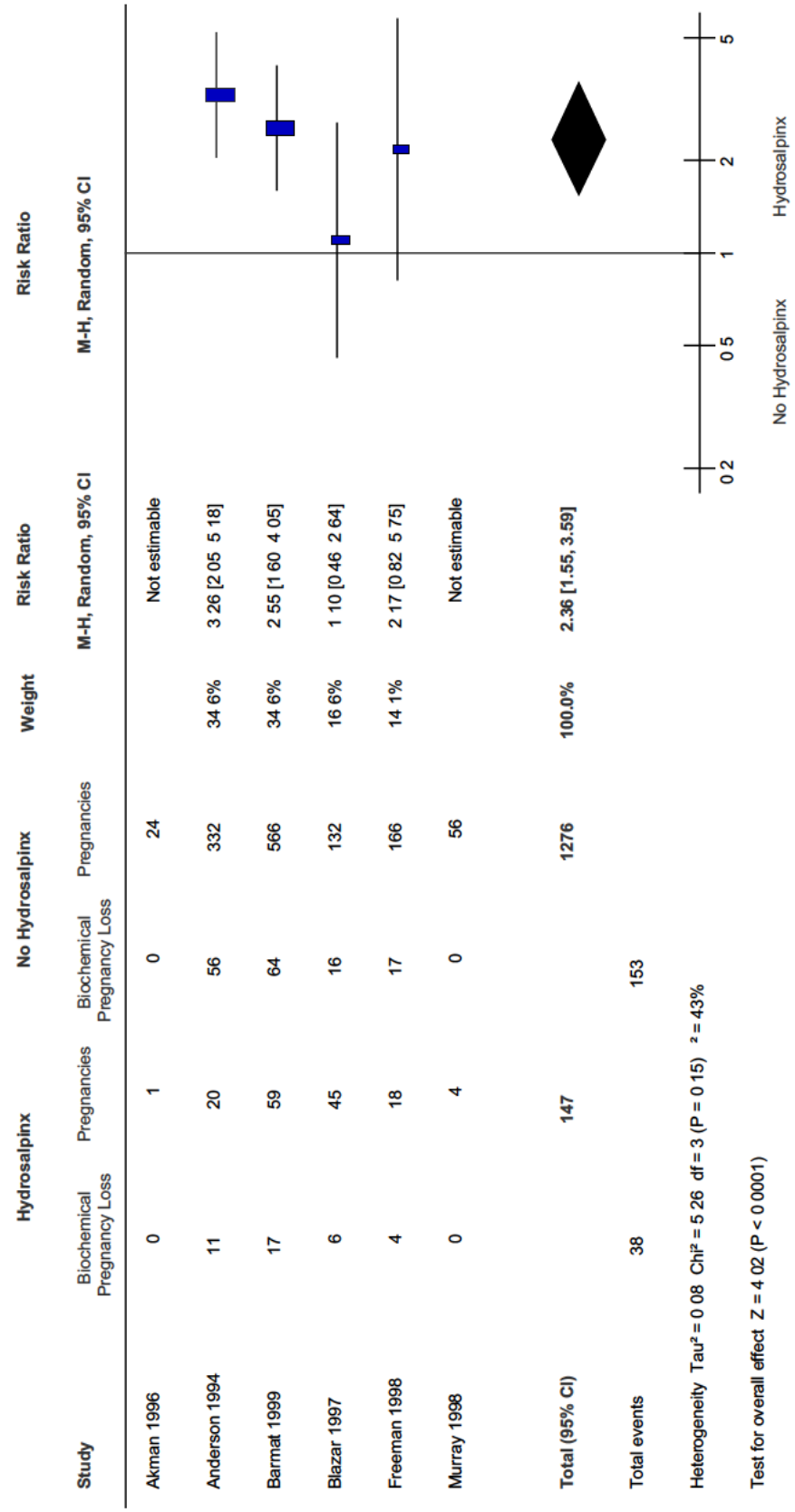


Figure 10: Meta-analysis of studies comparing biochemical pregnancy loss in women who had a hydrosalpinx to women who did not have a hydrosalpinx

Biochemical pregnancy loss in women with and without treatment for hydrosalpinx

Three studies (one randomised and two observational studies) compared biochemical pregnancy loss for treated women (any intervention) to untreated women. A meta-analysis of the risk ratios from these three studies shows minimal difference in biochemical pregnancy loss between these groups (RR 1.21; 95% CI 0.45–3.28) with no statistical heterogeneity (I^2 = 0%) (Figure 11).

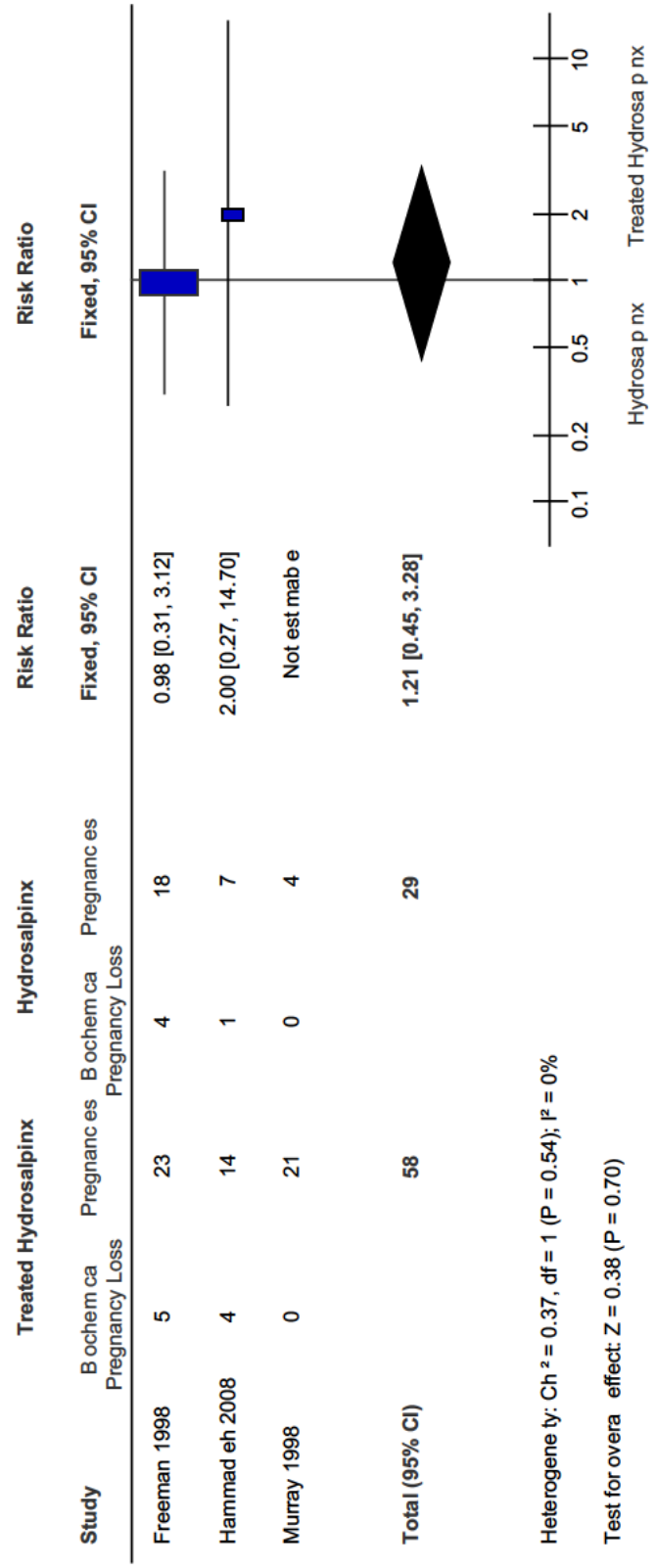


Figure 11: Meta-analysis of studies comparing biochemical pregnancy loss in women who had treatment (all interventions) for hydrosalpinx to women who did not undergo treatment for hydrosalpinx

Clinical pregnancy loss in women with and without hydrosalpinx

Clinical pregnancy loss was reported separately to total pregnancy loss in ten studies all of which were observational. Meta-analysis of these ten studies shows no difference for the pregnancy loss risk for women who had a hydrosalpinx versus women who did not (RR 1.14; 95% CI 0.83–1.58) (Figure 12). The increase in risk of clinical pregnancy loss is less than the increase in risk of biochemical pregnancy loss when comparing the same groups of women.

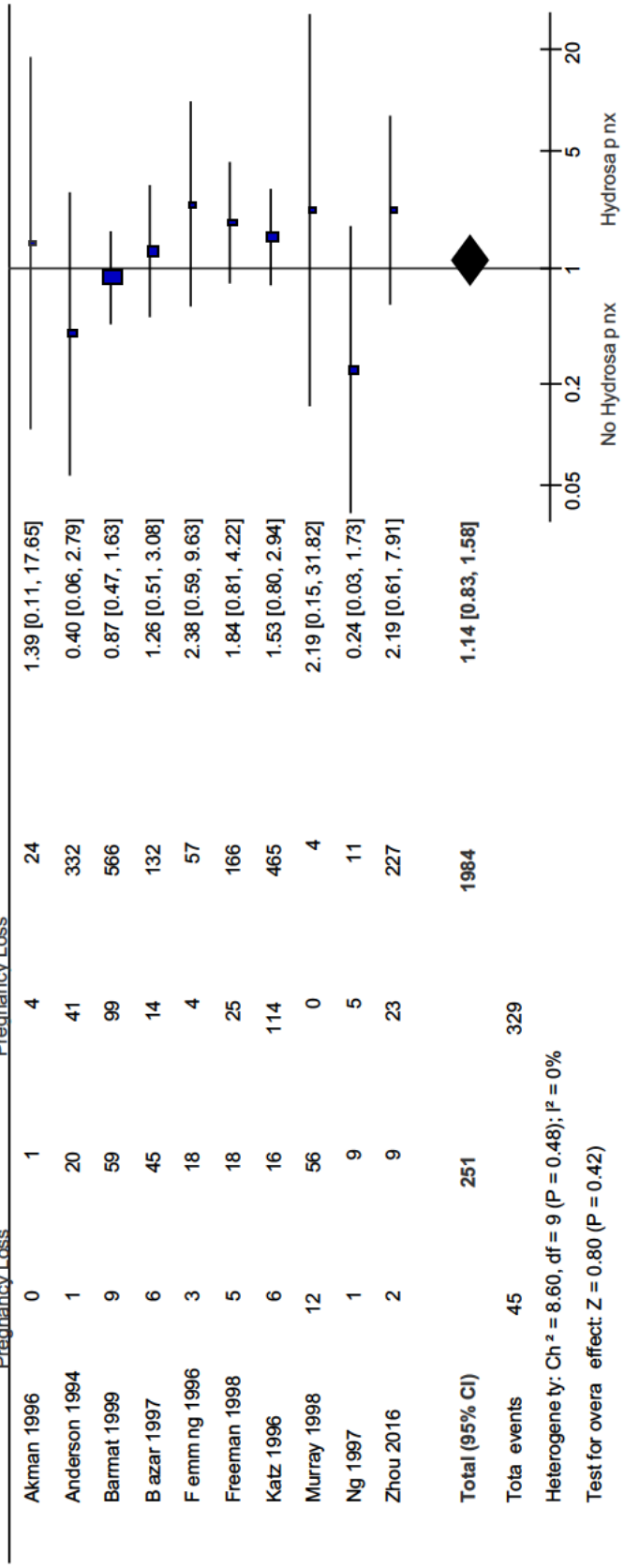


Figure 12: Meta-analysis of studies comparing clinical pregnancy loss in women who had a hydrosalpinx to women who did not have a hydrosalpinx

Clinical pregnancy loss in women with and without treatment for hydrosalpinx

11 studies (five randomised and six observational studies) specifically reported clinical pregnancy loss in women who had received treatment for their hydrosalpinx (all interventions) versus women with no treatment for their hydrosalpinx. Meta-analysis of these 11 studies shows that treatment of a hydrosalpinx reduced the clinical pregnancy loss risk by over half (RR 0.45; 95% CI 0.30–0.66) (Figure 13).

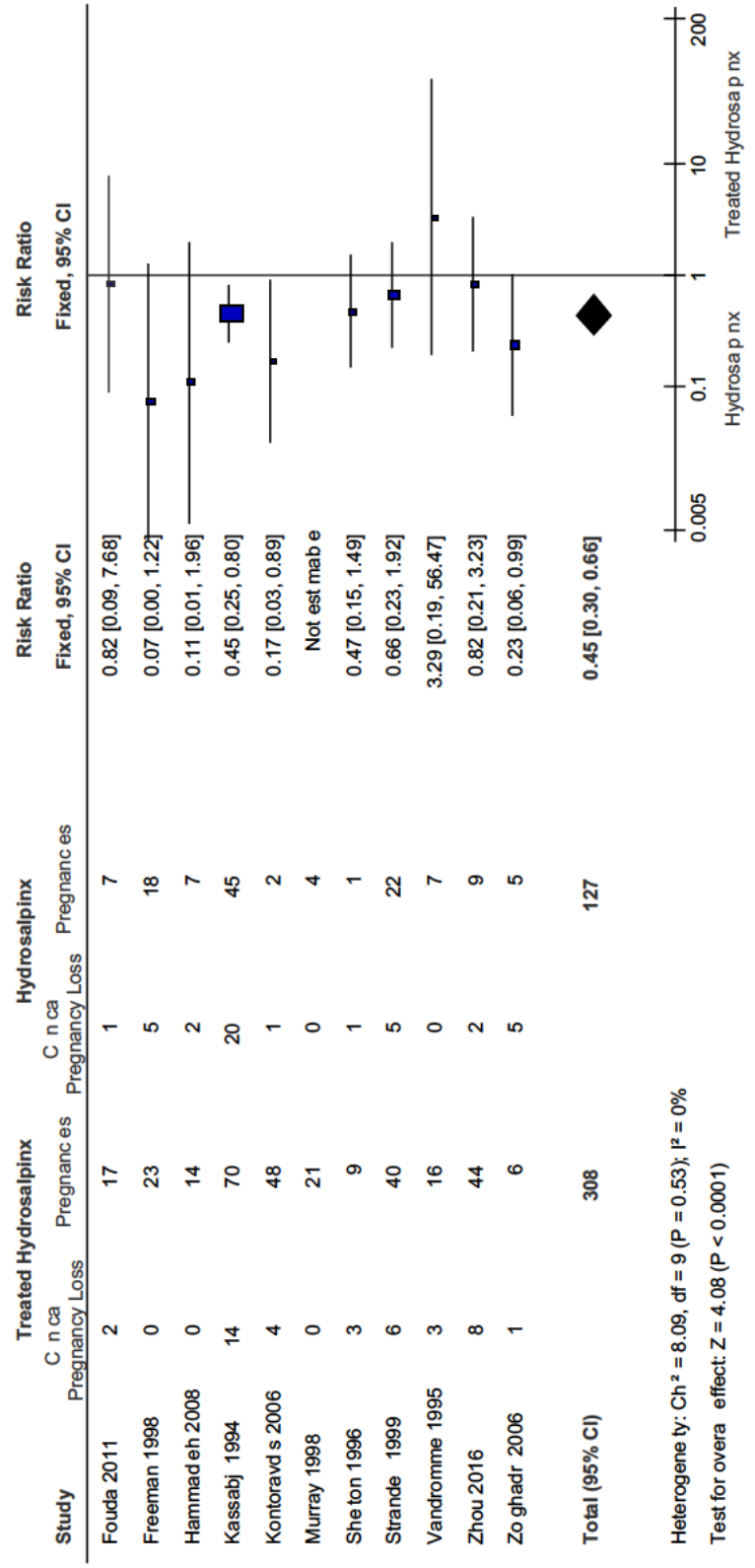


Figure 13: Meta-analysis of studies comparing clinical pregnancy loss in women who had treatment (all interventions) for hydrosalpinx to women who did not undergo treatment for hydrosalpinx

Ectopic pregnancy in women with and without hydrosalpinx

Ectopic pregnancy as an outcome was reported in 12 studies (all were observational studies). Meta-analysis shows a big rise for the ectopic pregnancy risk in women who had a hydrosalpinx versus women who did not (RR 3.27; 95% CI 1.72–6.23) with no severe statistical heterogeneity (I^2 = 41%) (Figure 14).

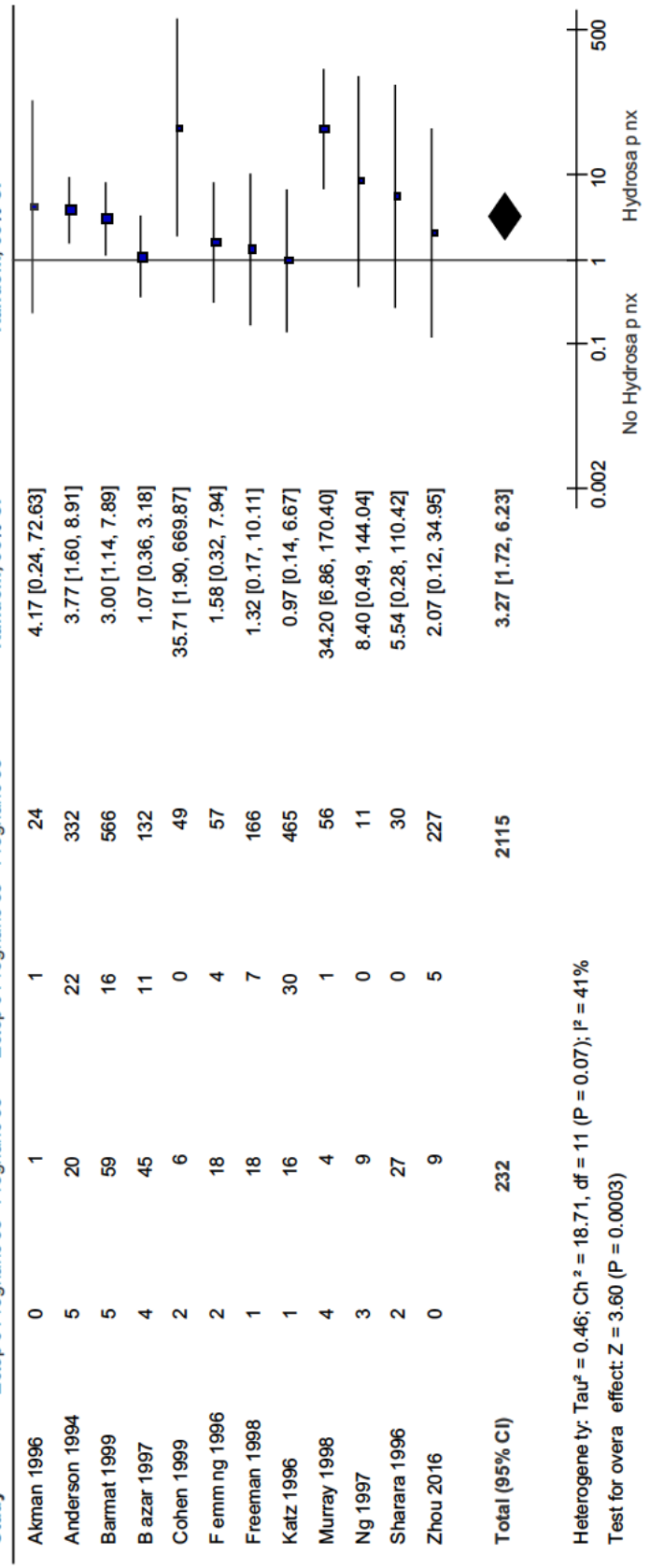


Figure 14: Meta-analysis of studies comparing ectopic pregnancy loss in women who had a hydrosalpinx to women who did not have a hydrosalpinx

Ectopic pregnancy in women with and without treatment for hydrosalpinx

Ectopic pregnancy as an outcome was also reported in 13 studies comparing women with treated hydrosalpinx to those with a hydrosalpinx. Meta-analysis shows a large decrease for the risk of an ectopic pregnancy in women who had a hydrosalpinx treated (all interventions) compared to women with no treatment for their hydrosalpinx (RR 0.30; 95% CI 0.15–0.62) (Figure 15). The reduction in risk varied by intervention with no difference from USS-guided aspiration of hydrosalpinges sub-group (RR 0.55; 95% CI 0.09–3.29). Salpingectomy reduced the risk of an ectopic pregnancy by a greater degree but overall, no difference was shown (RR 0.37; 95% CI 0.13–1.06). However, a clear difference was seen in the tubal conservational surgery subgroup (RR 0.15; 95% CI 0.05–0.49) with no statistical heterogeneity across the entire meta-analysis (I^2 = 0%) (Figure 15).

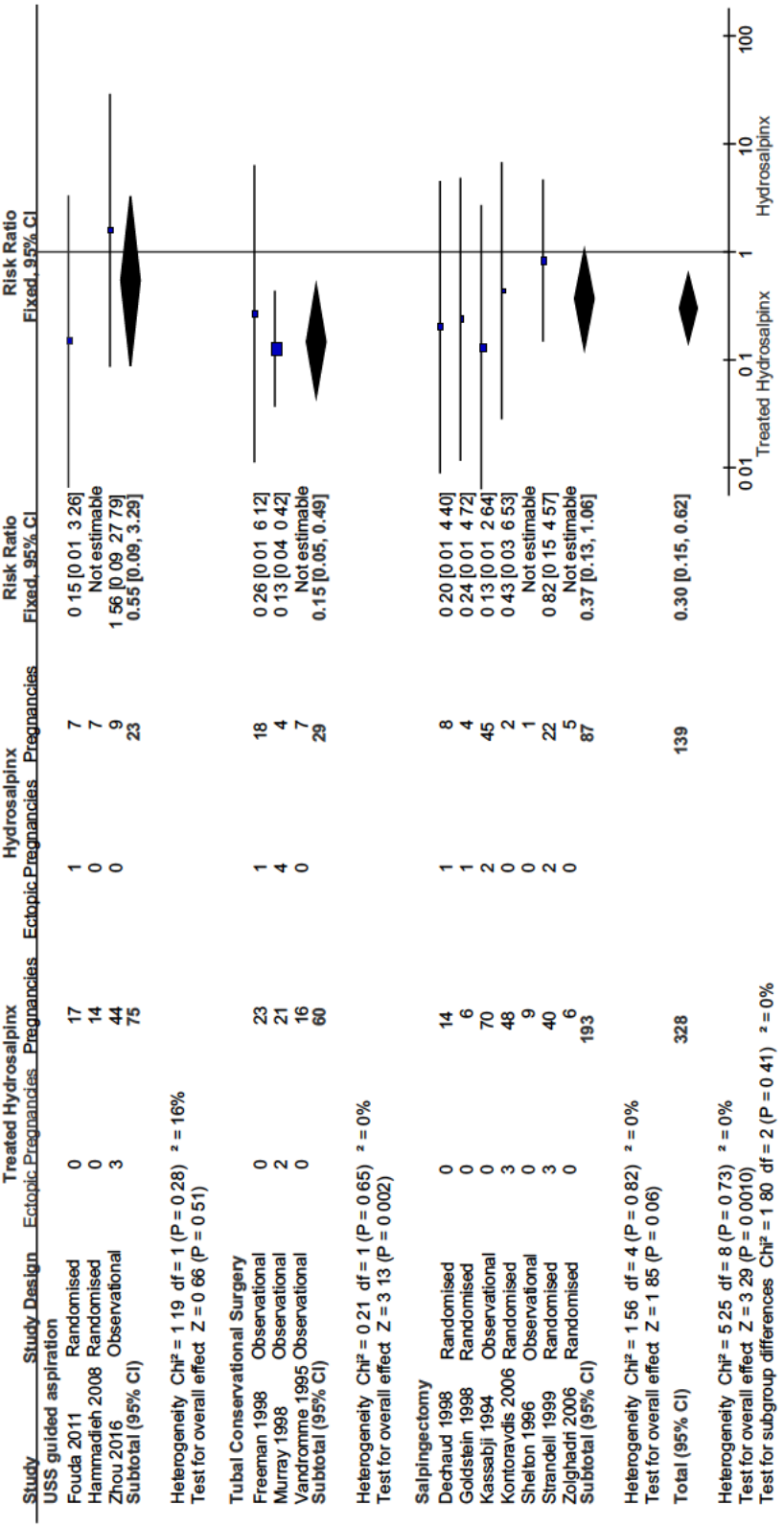


Figure 15: Meta-analysis of studies comparing ectopic pregnancy loss in women who had treatment for hydrosalpinx to women who did not undergo treatment for hydrosalpinx sub grouped according to treatment type

Discussion

Main findings

This systematic review and meta-analysis of 23 studies has demonstrated that for women who have a hydrosalpinx, the risk of pregnancy loss is increased. It further demonstrates that treatment of hydrosalpinx by tubal conservational techniques such as neosalpingostomy and salpingoplasty, and salpingectomy, can significantly reduce the risk of pregnancy loss. The risk of pregnancy loss with a hydrosalpinx appears to be greatest early on in a pregnancy. The risk of pregnancy loss when it is considered a biochemical pregnancy or is in the preclinical pregnancy stage is much higher than when a pregnancy is in the clinical pregnancy phase. It is also demonstrated that the risk of ectopic pregnancy is increased significantly in women with a hydrosalpinx. And that tubal conservational surgery or salpingectomy reduces this risk of ectopic pregnancy.

Strengths and limitations

This systematic review and meta-analysis has many strengths but also limitations which effect the ability to make concrete statements about the impacts of its findings. The methodological conduct for this review was robust. An extensive literature search strategy was used and advice from a data scientist was sought to ensure its meticulousness. No language or date restrictions were applied ensuring a high degree of confidence that all relevant studies in any language ever published were included. At least two independent authors reviewed all the retrieved references and were involved in both stages of study selection. Data extraction was

also checked by a second author ensuring accuracy. Two validated methods of quality assessment were used to examine the methodological conduct of the included studies.

However, limitations also exist. Only two of the observational studies were judged by the NOS of being of the highest quality with nine stars awarded and a further three were awarded eight stars. Several lower quality studies were, however, included with three studies given only four stars and four studies given five stars. It should be noted that the three lowest rated observational studies only contributed 12.3% of the data for the main meta-analysis of pregnancy loss in women with a hydrosalpinx versus women with no hydrosalpinx. The two highest rated studies contributed 12.2% of the data for this meta-analysis. The two largest studies which contributed most towards the main meta-analysis were, however, only awarded five stars and contributed more than a third of the data (33.7%).

Similarly, for the randomised studies, only two were judged by the RoB-2 tool to be at low risk of bias and the rest were judged to have either a high risk of bias or to have some concerns over the risk of bias. The two largest randomised trials which contributed 18.4% of the data for the second meta-analysis of women with a treated hydrosalpinx versus women with an untreated hydrosalpinx were both judged to have some concerns over their risk of bias. However, 32.8% of the data for this second meta-analysis on the treatment of hydrosalpinx was from an observational trial which was awarded eight stars on the NOS.

There was a small degree heterogeneity of the diagnostic criteria for the diagnosis of hydrosalpinges. We accepted the definitions that the studies themselves used and feel the heterogeneity that exists, makes our results more generalisable towards any commonly accepted definition of hydrosalpinx that is in use. We also felt there was significant overlap in the definitions the studies used so this is unlikely to have impacted on our findings significantly. Also, meta-analysis would not have been possible had we analysed each definition of hydrosalpinx separately. Finally, there is no globally accepted definition of a hydrosalpinx and whilst there may be more consensus currently due to the work of professional organisations, at the time of publication for many of these studies this was not the case.

Similarly, there was a degree of heterogeneity in terms of the definitions of the outcomes used and we accepted the definitions that the studies themselves used. We felt the heterogeneity that exists, makes our results more generalisable towards any commonly accepted definition of these outcomes that is in use. We also felt there was significant overlap in the definitions the studies used so this is unlikely to have impacted on our findings significantly. Also, meta-analysis would have resulted in less precise results had we analysed each definition of an outcome separately.

Hydrosalpinx amongst all the included papers has been treated as a binary variable with it either being present or absent; treated or untreated. The clinical reality may be of a gradient of disease severity, particularly in patients with unilateral or bilateral disease. This review was

therefore unable to examine the difference in affect between unilateral versus bilateral disease or of disease severity.

It should also be noted that the earliest included study for the main meta-analysis of pregnancy loss in women with a hydrosalpinx versus women without a hydrosalpinx was from 1994. All of the other included observational studies were also from the 90s decade apart from one in 2016. There have been significant advancements in ultrasound scanning technology and availability so we must question how applicable these results are to current clinical practice. This is less of an issue with the interventional trials as there is a spread of trials from 1994 to 2016 with trials from each of the decades beginning in 1990, 2000 and 2010. However, only 7.6% of the data for the second main-meta-analysis of pregnancy loss in women with a treated hydrosalpinx versus women with an untreated hydrosalpinx was from trials published in the last ten years. The surgical technology available will also have greatly advanced during this period meaning we must question the applicability to current practice. Reassuringly, however, there was little statistical heterogeneity for both of these meta-analyses perhaps indicating this advancement of technology has not had a significant impact on the findings.

Closely related is the fact that all the papers apart from one studied pregnancy loss in the assisted conception and IVF population. Perhaps meaning these results are much less applicable to the natural conception population. Assisted conception technology has also significantly advanced over the past 26 years. It is therefore also debateable how relevant and

comparable the papers published in the 90s are compared to more recent publications. However, similar mechanisms may play an adverse role in both populations, irrespective of the method of conception. The mechanism of adverse impact warrants further investigation which may elucidate new treatment strategies.

As discussed in my introduction to this thesis there are many risk factors for pregnancy loss which are confounding factors in trials. Many of these confounding factors were not stated and were not controlled, for example only one trial stated the previous number of pregnancy losses patients had suffered from. BMI was only stated in one study and smoking status was not mentioned in any studies. Significantly APS status was also not stated but this is likely due to the fact that evidence regarding its impact on pregnancy loss was only beginning to be established in the 90s. Age was a confounding factor which was discussed and attempted to be controlled for with the majority of studies limiting included women to those under the age of 40 as it has long been established the risk of miscarriage particularly due to chromosomal abnormalities increases with advancing age, this increased risk rises more significantly after the age of 35 (47). Where it was stated, mean age in all trials was less than 35 years old suggesting that age probably was adequately controlled for in this review. We accept that an upper age limit of 35 would have lessened any impact of age as a confounder but the individual studies did not allow us to perform sub-group analyses that we had initially planned to do.

Interpretation

The possible mechanisms for the results seen in this work have been discussed in section V of the introduction to this thesis and in the introduction to this chapter and this systematic review and meta-analysis was not designed to establish this. This work does, however, suggest hydrosalpinx is a risk factor for pregnancy loss and therefore clinicians working with early pregnancy services should be aware of this and counsel patients to this effect. Moreover, treatment of a hydrosalpinx should be considered in patients with unexplained pregnancy loss and concurrent hydrosalpinges. The best method of treatment for a hydrosalpinx has also not been clearly established which would need high-quality randomised trial evidence. And furthermore, research should investigate the benefit of testing for tubal function. This is because the possible mechanisms which have been postulated to be the cause of the negative affect of hydrosalpinges, may also affect pregnancies when tubes first become blocked, before the build-up of hydrosalpingeal fluid causes the swollen characteristic features of a hydrosalpinx.

The mechanism of adverse impact on a pregnancy during the pre-clinical phase of pregnancy and why its impact maybe greater than in the clinical phase is also unknown. The existing theories do not propose this difference in adverse impact depending upon the gestation of the pregnancy. It is conceivable that the physically larger the gestation is, the less of an impact that any mechanical impedance has to the pregnancy. We also know that the risk of miscarriage for any reason is higher the earlier the gestation of the pregnancy. Causes of miscarriage such as chromosomal and genetic abnormalities are unable to be controlled for

directly, although controlling for age could arguably indirectly do this, however, we were unable to perform the age subgroup analysis for reasons discussed earlier.

Conclusion

There is sufficient evidence to suggest that a hydrosalpinx is a risk factor for pregnancy loss particularly in the preclinical phase of a pregnancy and treatment of a hydrosalpinx may reduce this risk. The treatment of choice of a hydrosalpinx needs further randomised trial evidence before recommendations can be suggested.

CHAPTER THREE:

THE ROLE OF BLOCKED OR DAMAGED FALLOPIAN TUBES AND HYDROSALPINX IN RECURRENT MISCARRIAGE: A PROSPECTIVE COHORT STUDY OF PREVALENCE AND PROGNOSIS

Authors and contributions:

Dr Jayasish Ghosh conceived the concept, obtained ethical and other approvals, performed recruitment, the HyCoSy scans, collected the follow-up data, helped with statistical analysis and prepared the manuscript, tables and figures.

Dr Justin Chu helped obtain ethical and other approvals and provided comments on the manuscript.

Dr Adam Devall helped obtain ethical and other approvals.

Sister Oonagh Pickering helped with recruitment, the HyCoSy scans and collecting the follow-up data.

Rachael Boothe helped with recruitment, the HyCoSy scans and collecting the follow-up data.

Dr Malcolm Price performed the statistical analysis

Dr Ioannis D Gallos co-conceived the concept, helped obtain ethical and other approvals and provided comments on the manuscript.

Prof Arri Coomarasamy co-conceived the concept and provided comments on the manuscript.

Abstract

Research Question

What is the prevalence of blocked fallopian tubes and hydrosalpinx in the recurrent miscarriage population and what is the prognosis of women with recurrent miscarriage and concurrent blocked tubes and hydrosalpinx?

Background

Systematic review and meta-analysis evidence has shown hydrosalpinx may be a risk factor for pregnancy loss. Tubal testing is not recommended for the investigation of women with recurrent pregnancy loss. It is not known how common tubal pathology is in this population of women. This study aims to establish the prevalence of blocked tubes and hydrosalpinx in the recurrent miscarriage population and the reproductive outcomes of women with blocked tubes and hydrosalpinx.

Methods

A prospective observational cohort study conducted at a recurrent miscarriage clinic in a large tertiary teaching hospital in the U.K. (Birmingham Women's Hospital, U.K.). One hundred and thirty-seven women with recurrent miscarriage were recruited between February 2018 and September 2019. Eighty-one women had hystero-salpingo-contrast-sonography to detect tubal pathology, and were followed-up for their reproductive outcomes for one year.

Results

The prevalence of any type of blocked fallopian tube in the recurrent miscarriage population is 36.7% (95% CI 26.1% to 48.3%). The prevalence of hydrosalpinx in the recurrent miscarriage population is 6.2% (95% CI 2.0% to 18.8%). Women with any type of blocked tubes have lower pregnancy rates than women with patent tubes (RR=0.68; 95% CI 0.44, 1.00, p=0.03). Women with any type of blocked tubes are also twice as likely to have a pregnancy loss (RR=2.01; 95% CI 1.08, 3.72, p=0.05) and are less than half as likely to have a live birth beyond 24 weeks of gestation (RR=0.38; 95% CI 0.13, 1.07, p=0.04) compared to women with patent tubes.

Conclusion

Blocked tubes are common in the recurrent miscarriage population. Women with blocked tubes may have lower pregnancy rates, higher pregnancy loss rates and lower live-birth rates than women with patent tubes. Fallopian tube testing could be considered in women with recurrent pregnancy loss.

Introduction

The term recurrent miscarriage has been defined in the introduction to this thesis. Whilst different definitions exist, I will be using the ESHRE definition from their 2017 guideline (7):

> *"A diagnosis of Recurrent Pregnancy Loss (RPL) could be considered after the loss of two or more pregnancies."*

The ESHRE definition of recurrent miscarriage was chosen as it is more current and was produced from a consensus from the guideline development group which was comprised of early pregnancy experts across Europe including representatives from the UK. This is compared to the RCOG definition (5), which dates from 2011, and the guideline itself does not state the process by which this definition was agreed. Furthermore, the clinic from which recruitment was planned for the study in this chapter used the ESHRE definition as part of its referral criteria and so we wanted the results to be applicable to the patient population that was seen in this clinic.

The prevalence of recurrent miscarriage, which depends upon whether it is defined as two or three consecutive pregnancy losses, is between one and three percent (44). Recurrent miscarriage is a deeply distressing condition for the women and couples it afflicts. Literature in this area is sparse although there has been a recent recognition of its importance. One third of women suffer from clinically significant depression (143) which is approximately double the rate that is found in the general population (144). Distressing symptoms affect a significant proportion of women with current miscarriage. Klock et al 1997 showed over nearly two thirds (65%) of women with recurrent miscarriage suffer from alterations of sleep patterns, 44%

suffered from changes in appetite, 62% experienced changes in weight and 59% had decreased libido (143).

Causes of recurrent miscarriage have been previously discussed in chapter one but include genetic, endocrine, anatomical, infectious, thrombotic, autoimmune and lifestyle aetiologies and yet 50% are still unexplained (5,44).

It has also been discussed in chapter one how critically important the fallopian tubes are, as the site of conception and how they can be damaged by a variety of pathologies and become blocked and eventually swollen, resulting in a hydrosalpinx. The introduction to chapter two also discussed how common hydrosalpinx is and that it has been well established that hydrosalpinx negatively affects pregnancy rates by reduced implantation (105,115).

Chapter two then went on to show that a tubal blockage leading to a hydrosalpinx increases the risk of a pregnancy loss and that treatment may reduce this risk. Screening for tubal patency and hydrosalpinx is not currently recommended by the RCOG or ESHRE in either of their guidelines in this area (5,7). Although some larger hydrosalpinx will be picked up on the routine ultrasound scan of the pelvis that is recommended, patency and smaller hydrosalpinx would not. Therefore, we must question whether women with recurrent miscarriage should be screened specifically for tubal patency and hydrosalpinx. This chapter aims to establish whether tubal blockage and hydrosalpinx is a problem in the cohort of women who suffer

from recurrent miscarriage by establishing the prevalence of tubal blockage and hydrosalpinx in the recurrent miscarriage population. And we also aim to provide further evidence of the negative affect of blocked tubes and hydrosalpinx on pregnancy rates and pregnancy loss rates by establishing the prognosis of these women.

Whilst the primary aim of this study is to establish the prevalence of blocked tubes and hydrosalpinx in the recurrent miscarriage population and their prognosis, inevitably other abnormalities will be seen on USS and so a discussion of all features and their USS definitions is necessary.

For hydrosalpinx, there are many definitions that exist and that have many common features. Osmers 2009 described a "longish cystic tumour, sometimes shaped like a corkscrew, with a smooth wall but without internal echoes" (145). Griffin 2013 described a "…a cystic lesion of tubular appearance within the pelvis. Small internally projecting nodules are compatible with the fimbriae and give the cyst a 'cogwheel' appearance…" (146). This 'cogwheel' appearance is explained by the mucosal folds of the lumen of the tube projecting inwards which, as the hydrosalpinx develops, become nodular and thick (147). These are but two definitions from radiology text books. Probably the most comprehensive definition is from the consensus statement by the Society of Radiologists in Ultrasound from the USA. They state that a hydrosalpinx, sonographically is "… a tubular shaped cystic mass with either short round projections (i.e., small nodules generally, 3 mm, also known as "beads on a string" appearance representing the endosalpingeal folds) or a waist sign (i.e., indentations on opposite sides).

The hydrosalpinx should be seen separate from the ipsilateral ovary. Incomplete septations may allow the imager to appreciate the tubular nature of the cyst." (148). This was the definition I used to diagnose a hydrosalpinx.

Any congenital uterine anomalies will be diagnosed and described according to the ESHRE and European Society for Gynaecological Endoscopy (ESGE) CONgenital UTerine Anomalies (CONUTA) classification system (149,150). This system describes abnormalities according to the table seven below.

Table 7: ESHRE/ ESGE CONUTA classification system for congenital uterine anomalies from (149,150).

UTERINE ANOMALY		
	Main Class	**Sub-class**
U0	Normal Uterus	
U1	Dysmorphic uterus	a. T -shaped b. Infantalis c. Others
U2	Septate uterus	a. Partial b. Complete
U3	Bicorporeal uterus	a. Partial b. Complete c. Bicorporeal
U4	Hemi-uterus	a. With rudimentary cavity (communicating or not horn) b. Without rudimentary cavity (horn without cavity/ no horn)
U5	Aplastic	a. With rudimentary cavity (bi- or unilateral horn) b. Without rudimentary cavity (bi- or unilateral uterine remnants/ aplasia)
U6	Unclassified malformations	
CERVICAL ANOMALY		
	Co-existent class	
C0	Normal cervix	
C1	Septate cervix	
C2	Double "normal" cervix	
C3	Unilateral cervical aplasia	
C4	Cervical aplasia	

VAGINAL ANOMALY	
	Co-existent class
V0	Normal vagina
V1	Longitudinal non-obstructing vaginal septum
V2	Longitudinal obstructing vaginal septum
V3	Transverse vaginal septum and/or imperforate hymen
V4	Vaginal aplasia

Uterine polyps would have been suspected based on the presence of an echogenic endometrial lesion with or without an interrupted mucosal sign or feeding vessel (151). Adenomyosis would have been suspected based on USS findings of the features described in table eight by the Morphological Uterus Sonographic Assessment (MUSA) group from the International Society of Ultrasound in Obstetrics & Gynaecology (ISUOG) (152).

Table 8: USS features of adenomyosis described by the MUSA group from (152)

Feature	Adenomyosis
Serosal contour of uterus	Often globally enlarged uterus
Definition of lesion	Ill-defined in diffuse adenomyosis (adenomyoma may be well-defined)
Symmetry of uterine walls	Myometrial anteroposterior asymmetry
Lesion: Outline	Ill-defined
Lesion: Shape	Ill-defined
Lesion: Contour	Irregular or ill-defined
Lesion: Rim	No rim
Lesion: Shadowing	No edge shadows, fan-shaped shadowing
Lesion: Echogenicity	Non-uniform: mixed echogenicity, cysts, hyperechogenic islands, sub-endometrial lines and buds
Lesion: Vascularity	Trans-lesional flow
Junctional zone (JZ): thickness, regularity	Thickened; irregular or ill-defined
JZ: interruption	Interrupted JZ (even in absence of localized lesions)

Endometriosis would have been suspected based on USS findings of the features described by the International Deep Endometriosis Analysis (IDEA) group from the ISUOG (153). These

include: sonographic presence of endometrioma, lack of ovarian mobility and presence of endometriotic nodules in surrounding viscera (153). Ovarian and adnexal pathology was categorised according to the sonographic features summarised by Sayasneh et al 2015 (154). Polycystic ovaries were diagnosed according to the Rotterdam Criteria (155). It should be noted that the newer criteria stated by the International PCOS Network had not been published at the time this study was started (156). Fibroids were categorised according to the subclassification system of leiomyomas from the PALM-COEIN classification described by Munro et al 2011 produced by the International Federation of Gynaecology and Obstetrics (FIGO) (157). For the purposes of this thesis, the different types of fibroid one to seven were grouped together. Types zero, one and two were described as submucosal. Types three and four were described as intramural. Types five, six, seven and eight were described as sub-serosal. Type two to five was described as hybrid.

Material and methods

Study design

This study was a prospective observational cohort study. The full study protocol is available in Appendix 1. All eligible women attending the Tommy's recurrent miscarriage clinic held at Birmingham Women's Hospital from 28th February 2018 to 11th September 2019 were approached for consent for recruitment. All patients attending the clinic were sent the trial patient information sheet (Appendix 2) through the post along with their appointment letter for the clinic. They were also given the patient information sheet when they attended for their appointment. The inclusion criteria were similar to the referral criteria of the clinic to ensure

applicability of the results to the population seen at recurrent miscarriage clinics. The inclusion criteria were women aged between and including 18 to 45 years old, a history of recurrent miscarriage (two or more pregnancy losses) and an ability to give informed consent. Exclusion criteria included an inability to have a HyCoSy performed, an inability to give consent or if the patient was pregnant. Reasons for an inability to have a HyCoSy may have included allergy to the contrast media or sonographic gel used for the HyCoSy, or anatomical anomalies or a cervical stenosis meaning the HyCoSy could not physically be performed.

After taking consent (Appendix 3), women had a test for *C. trachomatis* as per NICE guidance which is required prior to uterine instrumentation to reduce the risk of subsequent pelvic inflammatory disease (96). Their general practitioners were informed of their decision to take part in the study (Appendix 4). Patients were informed they could leave the study at any point without having to give a reason. They were then asked to contact the study team via telephone or email on the first date of their next menstrual period. Their HyCoSy was carried out as soon as possible after their menstruation ended and before they had unprotected sexual intercourse (UPSI) and always within the first ten days of their menstrual cycle. Should a woman not be having regular periods they were prescribed progestogens by their GP to induce menstruation before attending for HyCoSy. This was to avoid the risk of pregnancy and ensure the endometrium was as thin as possible so as not to impede the flow of the ultrasonographic contrast media and affect the quality of the HyCoSy. The expected sensitivity and specificity of HyCoSy has been discussed in chapter one. Due to the higher expected specificity of HyCoSy, if a normal result was obtained, no method of corroboration was pursued. If tubal

blockage was suspected on HyCoSy, due to the lower expected sensitivity of HyCoSy, then patients were offered a HSG to confirm findings. The results of the HSG and any clinical actions were then discussed by the patient's clinician in clinic. A normal result was noted if the echo-bright contrast agent was seen to be flowing through the fallopian tube and was seen flowing out of the fimbrial end or accumulating around the ipsilateral ovary. It must be noted that HyCoSy is a test for tubal patency and does not test for tubal function. Tubal function likely relies on a combination of endocrine secretions, coordinated action of cilia and coordinated neuromuscular activity, however, there are no established tests for tubal function, only tubal patency (158). A degree of patency is of course a necessary component of function.

A routine pelvic USS was carried out followed by canulation of the cervix and flushing of the contrast media through the cannula into the uterus and fallopian tubes. The passage of the contrast media was tracked in real time using an ultrasound machine to check for tubal patency. ExEm® foam, manufactured by de Smit medical UK, a purposed designed contrast agent for HyCoSy scans was used for all HyCoSys. A GIS catheter (GISCATHN970) also manufactured by de Smit Medical, UK was used to introduce the contrast agent for all HyCoSys. All HyCoSys were performed by myself, an RCOG trainee in obstetrics and gynaecology who has received specialist training in performing HyCoSy scans at the Wrightington Hospital, Wigan and University Hospitals Coventry and Warwickshire and has been assessed as competent at performing intermediate level gynaecological scans and HyCoSy scans independently.

Following their HyCoSy scans, women were informed of their results and continued their treatment at the Tommy's recurrent miscarriage clinic under their usual clinician. Outcome data was collected after 12 months manually by myself from physical paper medical notes or electronic patient records. Where data was incomplete or not available, patients were contacted via telephone and email. Where an ongoing pregnancy was reported at 12-months by the patient we subsequently re-contacted the patient to find out the final outcome of the pregnancy. It should be noted that due to the Covid-19 pandemic for four patients, the full 12 months after their HyCoSy had not elapsed since data collection was commenced early before the shutdown of non-essential NHS services.

We attempted to recruit 203 patients. For a prevalence survey in a condition where the prevalence is unknown, but it is not expected to be higher than 25% for obtaining a 95% level of confidence and precision at 0.05 we estimated that 184 patients are required. To account for up to a 10% level of attrition, 203 patients should have been recruited.

Statistical analysis

For the prevalence survey of blocked tubes and hydrosalpinx in the recurrent miscarriage population, data has been presented using descriptive statistics. For the comparison of the cohorts, we reported numbers of individuals at each stage of study e.g., numbers confirmed eligible, included in the study, attended for HyCoSy, completed HyCoSy, completed follow-up, and analysed. The reasons for non-participation at each stage have been described. We also described the characteristics of study participants (e.g., demographic, clinical) and potential

confounders (e.g., age, body mass index.) We indicated the number of participants with missing data for each variable of interest. We summarised follow-up time (e.g., average and total amount) and reported numbers of outcome events for each cohort. We reported unadjusted relative risk estimates and their precision (e.g., at the 95% confidence interval). Subgroup analyses were also performed according to the outcome of the HyCoSy. Other subgroup analyses such as for age, BMI, parity, excluding the first 50 patients and history of previous pelvic or sexually transmitted infection were also planned. Fisher's Exact test and the Mann-Whitney U test were used to calculate P values for categorical variables and continuous variables respectively.

Ethical and other approvals

Sponsorship of this study was granted by the University of Birmingham (RG_17-150) on 14th November 2017 (Appendix 5). Ethical approval was granted by the West Midlands Edgbaston Research Ethics Committee (IRAS ID: 232650, REC Reference: 17/WM/0444) and Health Research Authority (HRA) on 16th January 2018 (Appendix 6, 7 and 8). The research and development office of Birmingham Women's Hospital granted permission for this study on 16th February 2018 (R&D No: 17/BW/GYN/PO48) (Appendix 9). An amendment was also submitted to the protocol of this study with a minor alteration allowing self-swabbing for *C. trachomatis* on 3rd December 2018 (Appendix 10 to 14). This was accepted by the HRA on 8th August 2018 (Appendix 15). This study was also prospectively registered at Clinicaltrials.gov (NCT03703401) (Appendix 16). And given NIHR Portfolio status on 28th September 2018 (Appendix 17).

Results

Study participants

The flow of participants during the study is shown in figure 16. A total of 543 women between the 28th of February 2018 and 11th of September 2019 were provided information and approached for recruitment into the study at the Tommy's Recurrent Miscarriage clinic held at Birmingham Women's Hospital, Birmingham, U.K. A total of 137 (25.2%) women consented for recruitment into the study.

Of these, 81 women (59.1%) returned for a hystero-salpingo-contrast-sonogram (HyCoSy). Two women (2.5%) could not tolerate the HyCoSy due to discomfort and the procedure could not be completed and there was no result. Both declined the offer of another attempt at performing the HyCoSy with analgesia at a later date. Recruited women were asked to contact the study management team to schedule their HyCoSy immediately after their next menstrual period but before unprotected sexual intercourse (UPSI) had occurred in that menstrual cycle. We were unable to scan 55 (40.1%) of recruited women as they did not contact the study team at the appropriate time despite reminders. One woman (0.7%) requested to drop out of the study before having her HyCoSy.

Of the 79 women who completed the HyCoSy, follow-up data was obtained for 75 women (94.9%). We were unable to contact four (5%) of the women who were scanned, despite

multiple attempts using the contact details they had provided at recruitment. Of the 75 women for whom we obtained follow-up data, we obtained ten months of follow-up for one woman (1.3%) as we performed the follow-up earlier than planned due to redeployment of the study team due to the Covid-19 pandemic. When we attempted to re-contact her after the so-called first wave of the Covid-19 pandemic, we were unable to do so. We were also unable to obtain the final pregnancy outcome of three women (4.0%) for the same reason.

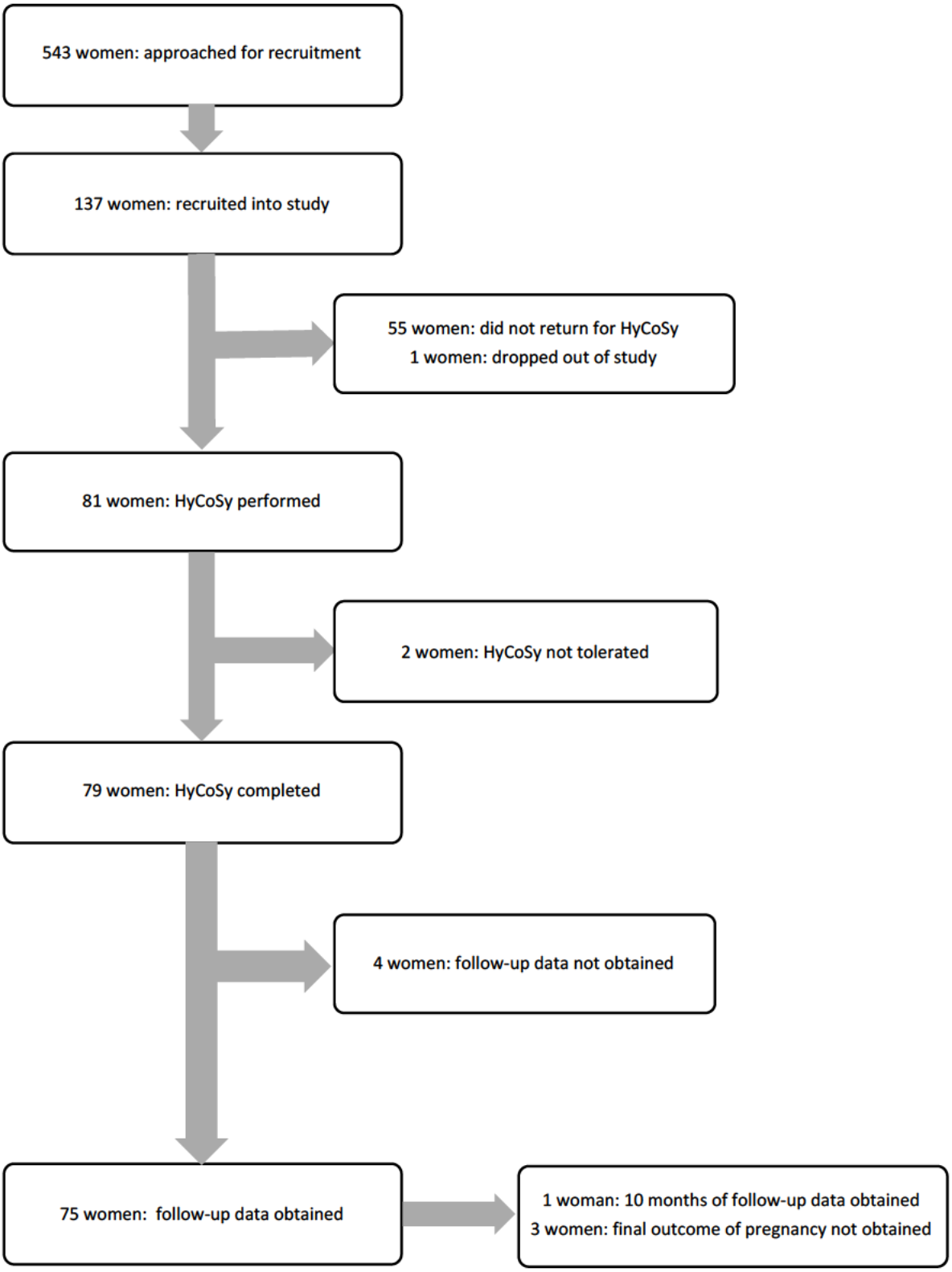


Figure 16: Flow chart of participants during study

Baseline characteristics

The full baseline characteristics of recruited women who had a completed HyCoSy are shown in table nine below. The mean age of the cohort of women with no blocked tubes (34.5 years (SD 4.8 years)), who are also referred to as cohort one, was similar to the cohort of women with at least one blocked tube on their HyCoSy (34.6 years (SD 4.9 years), who are also referred to as cohort two. The median Body Mass Index (BMI) across both cohorts was overweight, however, a higher proportion of the women in cohort two, had an obese BMI (41%) compared to cohort one (19%). In terms of ethnicity, both cohorts had similar proportions of white/European women (70% and 69%), however, cohort one had more than double the proportion of south Asian/ British south Asian women (24% versus 10%) and less than half the proportion of black/ black British (6% versus 14%) of cohort two.

There were similar proportions of women who had never smoked tobacco products (78% versus 76%), drank no alcohol (53% versus 55%) or less than or equal to two units of alcohol per day (41% versus 38%) across both cohorts. In terms of caffeine, this was also the case across both cohorts for women who drank no tea (38% versus 34%) or greater than or equal to one cup but less than or equal to seven cups of tea per week (24% versus 24%). In terms of coffee, there was a higher proportion of women who drank no coffee in cohort one (62% versus 45%). There was a similar proportion across both cohorts of women who drank no energy drinks or caffeinated fizzy drinks (74% versus 69%). In terms of previous pregnancy losses, both cohorts had the same median number of previous losses (3).

In terms of clinical risk factors for tubal damage, for sexually transmitted infections (STI), similar proportions in both cohorts had no previous infections (84% versus 79%) and C. *Trachomatis* (12% versus 10%). For clinical risk factors for miscarriage, overall, there were low numbers of women with risk factors. However, a higher proportion of women from cohort one had previously been diagnosed with antiphospholipid syndrome (APS) (10% versus 3.5%), had a family history of recurrent miscarriage (22% versus 14%) and had known cavity distorting fibroids (12% versus 6.9%) compared to cohort two.

Table 9: Baseline characteristics of recruited women who had a HyCoSy, grouped according to result of HyCoSy

Characteristic	No blocked tubes N=50 Cohort 1	At least 1 blocked tube N=29 Cohort 2
Maternal age – years	N=50	N=29
Mean (SD)	34.5 (4.8)	34.6 (4.9)
Median (IQR)	34 (31 – 38)	34 (32 – 38)
Maternal BMI – kilograms/meters squared (Kg/m^2)	N=47	N=29
Median	25.6 (21.6-29.4)	28.3 (24.3,33.1)
Maternal BMI >30 – no. (%)	9 (19%)	12 (41%)
Maternal ethnicity – no. (%)	N=50	N=29
White/ European	35 (70%)	20 (69%)
South Asian/ British South Asian	12 (24%)	3 (10%)
Black/ Black British	3 (6%)	4 (14%)
South East Asian/ British South East Asian	0 (0%)	0 (0%)
Mixed heritage	0 (0%)	1 (3.5%)
Other	0 (0%)	1 (3.5%)
Maternal smoking status – no. (%)	N=50	N=29
No information	0 (0%)	0 (0%)
Never smoked	39 (78%)	22 (76%)
Ex-smoker	3 (6%)	3 (10%)
≤ 5 cigarettes/ day	4 (8%)	1 (3.5%)
> 5 but ≤ 10 cigarettes/ day	1 (2%)	2 (6.9%)
>10 but ≤ 20 cigarettes/ day	3 (6%)	1 (3.5%)
>20 cigarettes/ day	0 (0%)	0 (0%)
Other tobacco products	0 (0%)	0 (0%)
Vaping products	0 (0%)	0 (0%)

Maternal alcohol use – no. (%)	N = 49	N=29
No information	1 (2%)	0 (0%)
None	26 (53%)	16 (55%)
≤ 2 units/ day	20 (41%)	11 (38%)
> 2 but ≤ 4 units/ day	1 (2%)	2 (6.9%)
> 4 but ≤ 10 units/ day	1 (2%)	0 (0%)
> 10 units/ day	0 (0%)	0 (0%)
Maternal caffeine consumption		
Cups of caffeinated tea drunk per week – no. (%)	N=50	N=29
No information	1 (2%)	0 (0%)
0	19 (38%)	10 (34%)
≥1 but ≤7 cups	12 (24%)	7 (24%)
>7 but ≤14 cups	12 (24%)	6 (21%)
>14 but ≤28 cups	5 (10%)	5 (17%)
>28 cups	1 (2%)	1 (3.5%)
Cups of caffeinated coffee drunk per week – no. (%)	N=50	N=29
No information	1 (2%)	0 (0%)
0	31 (62%)	13 (45%)
≥1 but ≤7 cups	8 (16%)	7 (24%)
>7 but ≤14 cups	5 (10%)	6 (21%)
>14 but ≤28 cups	4 (8%)	2 (6.9%)
>28 cups	1 (2%)	1 (3.5%)
Cans of energy drink/ caffeinated fizzy pop drunk per week – no. (%)	N=50	N=29
No information	1 (2%)	0 (0%)
0	37 (74%)	20 (69%)
≥1 but ≤7 cans	6 (12%)	7 (24%)
>7 but ≤14 cans	2 (4%)	0 (0%)
>14 but ≤28 cans	4 (8%)	2 (6.9%)
>28 cans	0 (0%)	0 (0%)
Parity – Median (IQR)	N=50	N=29
Previous live birth ≥ 24 weeks	0 (0 - 1)	0 (0 - 0)
Previous still birth ≥ 24 weeks	0 (0 - 0)	0 (0 - 0)
Previous miscarriage < 24 weeks but > 14 weeks	0 (0 - 0)	0 (0 - 0)
Previous pregnancy loss ≤ 14 weeks	3 (2 - 4)	3 (2 - 3)
Previous ectopic pregnancy	0 (0 - 0)	0 (0 - 1)
Previous termination for any reason	0 (0 - 0)	0 (0 - 0)
Sexually transmitted infection/ diseases – no. (%)	N=50	N=29
No information	0 (0%)	0 (0%)
No STI/STD	42 (84%)	23 (79%)
Chlamydia	6 (12%)	3 (10%)
Gonorrhoea	0 (0%)	1 (3.5%)
Chlamydia & Gonorrhoea	0 (0%)	0 (0%)
Other STI/STD	2 (4%)	2 (6.9%)
Clinical risk factors – no. (%)	N=50	N=29
Previous methotrexate treatment for ectopic pregnancy	3 (6%)	3 (10%)
Previous salpingectomy or other tubal surgery for ectopic pregnancy	0 (0%)	7 (24%)
Previous tubal surgery of any type for fertility purposes	1 (2%)	2 (6.9%)
Previous tubal surgery for any other reason	1 (2%)	0 (0%)

Polycystic ovarian syndrome	5 (10%)	3 (10%
Family history of recurrent miscarriage	11 (22%)	4 (14%)
Diagnosis of antiphospholipid syndrome (APS)	5 (10%)	1 (3.5%)
Previous large-loop excision of the cervical transformation zone (LLETZ)	4 (8%)	1 (3.5%)
Poorly controlled diabetes mellitus	0 (0%)	0 (0%)
Poorly controlled thyroid disease	0 (0%)	1 (3.5%)
Known cavity distorting fibroids	6 (12%)	2 (6.9%)
Known endometriosis or adenomyosis	1 (2%)	0 (0%)
Known tubal disease	3 (6%)	1 (3.5%)
Known congenital uterine abnormality	1 (2%)	0 (0%)
Known inherited thrombophilia	3 (6%)	1 (3.5%)

Non-tubal abnormalities

The full results of the HyCoSy scan for non-tubal abnormalities is shown in table 10 below. Of the 79 women who had a completed HyCoSy scan, 50 women (63.3%) had no blocked tubes (cohort one) and 29 women (36.7%) had at least one blocked tube of any type (cohort two). There was a higher proportion of women with sonographic evidence of congenital uterine anomalies in cohort two (17% versus 2%). The one congenital uterine anomaly found in cohort one was a Class U3a C0 V0 partial dysfused uterus. The anomalies found in cohort two were: a Class U3a C0 V0 partial dysfused uterus, a Class U4b C0 V0 unilaterally formed uterus with an aplastic rudimentary horn, a Class U2a C0 V0 partial septate uterus and two Class U1c C0 V0 arcuate uteruses.

There was no evidence of endometrial pathology in cohort two with at least one blocked tube but four women had sonographic appearances of a polyp in cohort one with patent tubes. Approximately half the women in cohort two with at least one blocked tube had sonographic evidence of adenomyosis but only a third in cohort one. Minimal sonographic evidence of

endometriosis was seen in either group. In terms of ovarian and adnexal pathology, the majority in both groups had nil. However, almost a quarter of women in cohort two with at least one blocked tube had sonographic appearances of polycystic ovaries (PCO) compared to 8% in cohort one. There were small numbers of other pathologies seen such as simple cysts, haemorrhagic cysts, pseudocysts and para-tubal or para-ovarian cysts in both groups. There were no other complex cysts seen in either group. Only a few women had sonographic evidence of leiomyomas, two women had intramural fibroids seen in cohort one with patent tubes. And three women had intramural and subserous or pedunculated leiomyomas seen respectively in cohort two with at least one blocked tube. No hybrid leiomyomas were seen.

Table 10: Non-tubal abnormalities seen on HyCoSy, grouped according to result of HyCoSy

Abnormality	No blocked tubes N=50 Cohort 1	At least 1 blocked tube N=29 Cohort 2
USS evidence of congenital uterine anomaly – no. (%)	1 (2%)	5 (17%)
USS evidence of polyps/ other endometrial pathology – no. (%)	4 (8%)	0 (0%)
USS evidence of adenomyosis – no. (%)	16 (32%)	15 (52%)
USS evidence of endometriosis or endometrioma – no. (%)	1 (2%)	0 (0%)
Ultrasound evidence of other ovarian/ adnexal pathology – no. (%)	N=50	N=29
Nil	42 (84%)	15 (52%)
Polycystic ovaries	4 (8%)	7 (24%)
Simple cysts	1 (2%)	2 (7%)
Haemorrhagic cysts	2 (4%)	3 (10%)
Dermoid cysts	0 (0%)	0 (0%)
Other complex cysts	0 (0%)	0 (0%)
Para-tubal or para-ovarian cysts	0 (0%)	2 (7%)
Pseudocysts	1 (2%)	0 (0%)
Pelvic kidneys	0 (0%)	0 (0%)
Appendiceal or diverticular abscess	0 (0%)	0 (0%)
Ultrasound evidence of leiomyomas – no. (%)	N=50	N=29
Sub-mucous leiomyomas	0 (0%)	0 (0%)
Intramural leiomyomas	2 (4%)	3 (10%)
Sub-serous or pedunculated leiomyomas	0 (0%)	3 (10%)
Hybrid leiomyomas	0 (0%)	0 (0%)

Tubal abnormalities

Out of 79 women who completed a HyCoSy scan, 29 had at least one blocked tube (36.7%, 95% CI 26.1% to 48.3%). Out of 81 women who attended for a HyCoSy scan, five had the sonographic appearances of a hydrosalpinx (6.2%, 95% CI 2.0% to 18.8%). Of the 29 women who had a blocked tube detected, 15 (51.7%) had a single blocked tube, 14 (48.3%) had two blocked tubes. This means out of 79 women who completed a HyCoSy scan, 19.0% had one blocked tube and 17.7% had two blocked tubes. In the group of women with one blocked tube, the blockage appeared sonographically to be proximal in most 13/15 (86.6%). For the group of women with two blocked tubes again, the blockage appeared sonographically to be proximal in most tubes 27/28 (96.4%).

Prognosis

The full results of the follow up for all women who completed their HyCoSy scan are presented in table 11. We obtained follow-up for 46 women out of 50 (92%) in the group of women who had no blocked tubes (cohort one). We obtained follow-up for 29 women out of 29 (100%) in the group of women who had at least one blocked tube (cohort two). There was no significant difference in the proportion of women who were actively trying for a pregnancy between the two cohorts at the point of follow-up (Relative risk (RR) 0.97; 95% Confidence interval (CI) 0.81, 1.15, p=0.73). Reasons that women were not actively trying for a pregnancy included, “taking a break from trying as it is exhausting”, for “mental-health” reasons, they had “given

up on having further children", they "wanted to focus on their career and wedding" or because they were awaiting further medical treatment such as appointments with clinical genetics. One woman with a blocked tube and a hydrosalpinx was awaiting surgical treatment for her tubal disease.

In those women who were actively trying for a pregnancy, the median number of months they were trying for, in cohorts one and two, were 7 (interquartile range (IQR) 4,11) and 10 (IQR 7,12) respectively, however, this difference was statistically significant (p=0.04). The majority of women in both cohorts one and two were trying naturally with regular unprotected sexual intercourse (UPSI) 34/41 (83%) and 23/25 (92%) respectively. The remainder were trying with IVF/ICSI, ovulation induction combined with UPSI or a combination of UPSI and IVF/ICSI. There was no use of intrauterine insemination (IUI). The difference between cohorts was not significant (p=0.62)

Women in cohort two, with at least one blocked tube had lower pregnancy rates compared to women in cohort one with no blocked tubes (RR 0.68; 95% CI 0.44, 1.00) which was a significant difference (p=0.03). This despite women in cohort two trying actively for pregnancy, for fewer months compared to cohort one. There was no significant difference between the two cohorts for women who had two or more positive pregnancy tests (RR 1.09; 95% CI 0.44, 2.70, p=1.00).

Women in cohort two, with at least one blocked tube, were more than 100% more likely to suffer from a pregnancy loss at less than or equal to 14 weeks of gestation, in their first pregnancy after their HyCoSy, compared to women in cohort one (RR 2.01; 95% CI 1.08, 3.72, p=0.05). Women in cohort two, with at least one blocked tube, were also less likely to have a live birth at greater than or equal to 24 weeks of gestation, in their first pregnancy after their HyCoSy, compared to women in cohort one (RR 0.38; 95% CI 0.13, 1.07, p=0.05) who had patent tubes. There was no significant difference between the two cohorts for having a term live birth (RR 1.21; 95% CI 0.97, 1.51, p=1.00).

As there were only five hydrosalpinges found, the reproductive outcomes for these women are described narratively. Only one woman, after counselling from her usual clinician, opted for tubal surgery, which did not occur during the period she was followed-up and she did not try to conceive during that time. One woman only tried to conceive for four months as she had a new job and did not conceive during that time. Two women tried to conceive for 12 months after their HyCoSy but did not achieve a pregnancy. The final woman tried to conceive for 10 months and did not achieve a pregnancy. We only obtained 10 months of follow-up for this woman for reasons outlined previously. Due to the small number of hydrosalpinges found, we cannot draw conclusions from this study regarding the prognosis of women with recurrent miscarriage and concurrent hydrosalpinx.

Table 11: Follow-up outcomes from women who completed a HyCoSy, no blocked tube versus at least one blocked tube, main analysis

Outcome	No blocked tubes Cohort 1	At least 1 blocked tube Cohort 2	Relative Risk (95% CI)	P Value
Actively trying for a pregnancy - no./total no. (%)	41/46* (89%)	25/29 (86%)	0.97 (0.81,1.15)	0.73
No. of months actively trying for a pregnancy since HyCoSy	N=41	N=25		
Median (IQR)	7 (4 to 11)	10 (7 to 12)		0.04
Method of trying for a pregnancy – no. (%)	N=41	N=25		
Natural (UPSI)	34 (83%)	23 (92%)		
IVF/ ICSI	5 (12%)	1 (4%)		
IUI	0 (0%)	0 (0%)		0.62
Both Natural and IVF	1 (2.4%)	1 (4%)		
Ovulation induction (e.g., clomid)	1 (2.4%)	0 (0%)		
Positive pregnancy tests since HyCoSy – no. (%)	N=41	N=25		
Any positive pregnancy test	32 (78%)	13 (52%)	0.68 (0.44, 1.00)	0.03
≥2 positive pregnancy tests	9 (22%)	6 (24%)	1.09 (0.44, 2.70)	1.00
No. of months after HyCoSy became pregnant	N=32	N=13		
Median (IQR)	4 (2 to 6)	2 (1 to 4)		0.14
Outcome of first pregnancy – no. (%)	N=29**	N=13		
Pregnancy loss ≤14 weeks	10 (34%)	9 (69%)	2.01 (1.08, 3.72)	0.05
Pregnancy loss >14 but < 24 weeks	0 (0%)	0 (0%)		
Still birth ≥ 24 weeks	0 (0%)	0 (0%)		
Ectopic pregnancy	0 (0%)	1 (8%)		
Termination of pregnancy	2 (6.9%)	0 (0%)		
Live birth ≥ 24 weeks	17 (59%)	3 (23%)	0.38 (0.13, 1.07)	0.05
Outcomes for women with a live birth ≥ 24 weeks gestation	N=17	N=3		
Live birth after 37 weeks 0 days of Gestation – no. (%)	14 (82%)	3 (100%)	1.21 (0.97, 1.51)	1.00

*We were unable to contact four women to obtain their follow-up

**We were unable to obtain the final pregnancy outcome for three women

Prognosis subgroup analyses

We performed two subgroup analyses to examine if there were differences between the pregnancy outcomes of the women with one blocked tube compared to two blocked tubes. These were compared to the no blocked tubes group.

The full results for the follow-up for no blocked tubes compared to one blocked tube subgroup analysis are presented in table 12. There was no significant difference in the proportion of women who were actively trying for a pregnancy between the two groups at the point of follow-up (RR 0.97; 95% CI 0.78, 1.21, p=1.00). The difference between the groups for the median number of months women were actively trying for a pregnancy since their HyCoSy was not significant (p=0.07). The majority of women in both groups used natural methods (UPSI) to try to conceive following their HyCoSy and the difference between groups was not significant (p=0.61). Similar to the overall analysis, women with one blocked tube appeared to have less positive pregnancy tests compared to women with patent tubes (RR 0.59; 95% CI 0.32, 1.09, p=0.04). And women with one blocked tube appeared to have a significantly higher risk of pregnancy loss at less than or equal to 14 weeks of gestation compared to women with patent tubes (RR 2.42; 95% CI 1.30, 4.48, p=0.06). There were no live births in the one blocked tube group.

Table 12: Follow-up outcomes from women who completed a HyCoSy, no blocked tubes versus one blocked tube, subgroup analysis

Outcome	No blocked tubes	1 blocked tube	Relative Risk (95% CI)	P Value
Actively trying for a pregnancy – no./total no. (%)	41/46 (89%)	13/15 (87%)	0.97 (0.78,1.21)	1.00
No. of months actively trying for a pregnancy since HyCoSy	N=41	N=13		

Median (IQR)	7 (4 to 11)	9 (7 to 12)		0.07
Method of trying for a pregnancy	N = 41	N = 13		
Natural (UPSI)	34 (83%)	13 (100%)		
IVF/ ICSI	5 (12%)	0 (0%)		
IUI	0 (0%)	0 (0%)		0.61
Both Natural and IVF	1 (2.4%)	0 (0%)		
Ovulation induction (e.g., clomid)	1 (2.4%)	0 (0%)		
Positive pregnancy tests since HyCoSy – no. (%)	N=41	N=13		
Any positive pregnancy test	32 (78%)	6 (46%)	0.59 (0.32, 1.09)	0.04
≥2 positive pregnancy tests	9 (22%)	3 (23%)	1.05 (0.33, 3.13)	1.00
No. of months after HyCoSy became pregnant	N=32	N=6		
Median (IQR)	4 (2 - 6)	2.5 (2 - 3)		0.11
Outcome of first pregnancy – no. (%)	N=29*	N=6		
Pregnancy loss ≤14 weeks	10 (34%)	5 (83%)	2.42 (1.30,4.48)	0.06
Pregnancy loss >14 but < 24 weeks	0 (0%)	0 (0%)		
Still birth ≥ 24 weeks	0 (0%)	0 (0%)		
Ectopic pregnancy	0 (0%)	1 (17%)		
Termination of pregnancy	2 (6.9%)	0 (0%)		
Live birth ≥ 24 weeks	17 (59%)	0 (0%)	-	-
Outcomes for women with a live birth ≥ 24 weeks gestation	N=17	N=0		
Live birth after 37 weeks 0 days of Gestation – no. (%)	14 (82%)	0 (0%)	-	-

* We were unable to obtain the final pregnancy outcome for three women

The full results for the follow-up for no blocked tubes compared to two blocked tubes subgroup analysis are presented in table 13. There was no significant difference in the proportion of women who were actively trying for a pregnancy between the two groups at the point of follow-up (RR 0.96; 95% CI 0.76, 1.22, p=0.66). The difference between the groups for the median number of months women were actively trying for a pregnancy since their HyCoSy was not significant (p=0.19). The majority of women in both groups used natural methods (UPSI) to try to conceive following their HyCoSy and the difference between groups was not significant (p=0.69). Interestingly, there was no real significant difference between

the two groups for any positive pregnancy tests (RR 0.75; 95% CI 0.45, 1.24, p=0.26) or two or more positive pregnancy tests (RR 1.14; 95% CI 0.36, 3.55, p=1.00). There was also no significant difference for the risk of pregnancy loss at less than or equal to 14 weeks of gestation (RR 1.66; 95% CI 0.73, 3.74, p=0.39) or for live-birth (RR 0.73; 95% CI 0.29, 1.81, p=0.68) between the two groups. These last four results are not consistent with the main analysis and first subgroup analysis.

Table 13: Follow-up outcomes from women who completed a HyCoSy, no blocked tubes versus two blocked tubes, subgroup analysis

Outcome	No blocked tubes	2 blocked tubes	Relative Risk (95% CI)	P Value
Actively trying for a pregnancy - no./total no. (%)	41/46 (89%)	12/14 (86%)	0.96 (0.76,1.22)	0.66
No. of months actively trying for a pregnancy since HyCoSy	N=41	N=12		
Median (IQR)	7 (4 to 11)	10 (7 to 12)		0.19
Method of trying for a pregnancy – no. (%)	N=41	N=12		
Natural (UPSI)	34 (83%)	10 (83%)		
IVF/ ICSI	5 (12%)	1 (8%)		
IUI	0 (0%)	0 (0%)		0.69
Both Natural and IVF	1 (2.4%)	1 (8%)		
Ovulation induction (e.g., clomid)	1 (2.4%)	0 (0%)		
Positive pregnancy tests since HyCoSy – no. (%)	N=41	N=12		
Any positive pregnancy test	32 (78%)	7 (58%)	0.75 (0.45,1.24)	0.26
≥2 positive pregnancy tests	9 (22%)	3 (25%)	1.14 (0.36,3.55)	1.00
No. of months after HyCoSy became pregnant	N=32	N=7		
Median (IQR)	4 (2 to 6)	2 (1 to 4)		0.61
Outcome of first pregnancy – no. (%)	N=29*	N=7		
Pregnancy loss ≤14 weeks	10 (34%)	4 (57%)	1.66 (0.73,3.74)	0.39
Pregnancy loss >14 but < 24 weeks	0 (0%)	0 (0%)		
Still birth ≥ 24 weeks	0 (0%)	0 (0%)		
Ectopic pregnancy	0 (0%)	0 (8%)		
Termination of pregnancy	2 (6.9%)	0 (0%)		
Live birth ≥ 24 weeks	17 (59%)	3 (43%)	0.73 (0.29,1.81)	0.68

Outcomes for women with a live birth ≥ 24 weeks gestation				
Live birth after 37 weeks 0 days of Gestation – no. (%)	14 (82%)	3 (100%)	1.21 (0.97,1.51)	1.00

* We were unable to obtain the final pregnancy outcome for three women

Discussion

Main findings

The prevalence of any type of blocked fallopian tubes in the recurrent miscarriage population is 36.7% (95% CI 26.1% to 48.3%). Of the women who had at least one blocked tube detected, 14 (48.3%) had two blocked tubes. The prevalence of hydrosalpinx in the recurrent miscarriage population is 6.2% (95% CI 2.0% to 18.8%). Women with any type of blocked tubes have lower pregnancy rates than women with patent tubes (RR 0.68; 95% CI 0.44, 1.00, p=0.03). Women with any type of blocked tubes are also twice as likely to have a pregnancy loss (RR 2.01; 95% CI 1.08, 3.72, p=0.05) and are less than half as likely to have a live birth beyond 24 weeks of gestation (RR 0.38; 95% CI 0.13, 1.07, p=0.04) compared to women with patent tubes. These differences were not present in the two blocked tubes subgroup analysis but were in the one blocked tube subgroup analysis.

Strengths, limitations and difficulties

This study has several strengths. To the best of our knowledge, this is the first study that has used tubal testing to detect patency and hydrosalpinx in this population of women. Many of our key results reached significance, reducing the risk that findings were due to chance. We also had a wide inclusion criterion ensuring our results were applicable to the population of women actually seen in recurrent miscarriage clinics. All HyCoSy scans were performed by the

same operator ensuring consistency of results and we used internationally recognised definitions and descriptions for sonographic outcomes. We obtained follow-up data for nearly 95% of women who completed their HyCoSy and this was obtained for 12 months after their HyCoSy.

We experienced some difficulties during the conduct of the trial. The overall recruitment proved to be more difficult than anticipated with a lower than planned number of women recruited from those eligible. It was also more difficult than anticipated to get recruited women back for their HyCoSy scan despite multiple reminders via text message, email and telephone calls. As the onus was on the participant to contact the study team at the appropriate time early in their cycle, we found women often forget to do this. We also found that as the referral to the Tommy's recurrent miscarriage clinic was automatic in cases of referrals from our early pregnancy unit after two miscarriages, women often were not as motivated to take part in research compared to the women who had sought out a referral from their general practitioner who tended to return for their scan at the appropriate time and needed no reminders. Women may also have been put off from participation as they had to return for a scan at their own time and financial cost (e.g., cost of travel, parking, child care, lost work). Financial recompense was unable to be provided. There were further difficulties due to the SARS-Cov-2 pandemic where by study staff were redeployed to essential frontline clinical areas. Overall, therefore our total number of women recruited and those scanned was lower than originally planned. This decreases the generalisability and confidence and power of our results which is reflected in the lack of statistical significance and wide confidence

intervals for some results. Statistically significant and clinically significant are of course different (159), so we believe a clear signal of association is shown.

We must also consider limitations. HyCoSy scans are based on an USS, which itself is affected in its quality, by individual patient factors such as faecal loading of the bowel, gaseous distension of the bowel, abdominal adiposity, pain experienced and BMI of the patient (160–163). And also, technical factors such as operator skill and experience, fallopian tube spasm, adequate cannulation of the cervix. Whilst direct visualisation of the fallopian tubes via laparoscopy and dye testing would have been the gold standard of testing tubal function and detecting hydrosalpinges, it would have been unethical to subject women to the risks associated with an invasive operation under general anaesthetic. It must be noted that HyCoSy is a recognised method of tubal testing with high sensitivity and specificity for tubal blockage and is therefore, from a research point of view, the most ethical method of tubal testing available for the aims of this study (164).

No confounders were excluded from the study population and therefore no confounders were able to be controlled for in the analyses presented but different subgroup analyses were planned to enable for them to be controlled. We had planned subgroup analyses based on age, BMI, parity, excluding the first 50 patients and history of previous pelvic or sexually transmitted infection as these are possible confounders. However, due to smaller than expected numbers recruited and numbers returning for scans, partially caused by the SARS-Cov-2 pandemic and the previously discussed difficulties, these subgroup analyses were not

possible as the subgroups would have had imprecise and non-significant results. We acknowledge that in women with a higher age, particularly greater than 40 years of age, the impact of accumulated genetic problems in the gametes could be a confounder, however, this would have been controlled for had we be able to perform the age subgroup analysis we had planned. Although from the baseline characteristics the median age of both groups from the main analysis was 34 so some reassurance can be taken about the impact of age on the results. The same can be said for other important confounders such as smoking, alcohol consumption, parity and previous STI. A final weakness would be that this study was observational in design and therefore only an association is able to be shown.

Interpretation

This study was not designed to establish a causal relationship but to provide further evidence of an association between tubal pathology and recurrent miscarriage and this, it has achieved. The possible mechanisms to explain why this association exists, have been discussed in detail in the introduction and discussion of chapter two. Women were not screened for chlamydial antibodies or the levels of titres of antibodies only current infection. The aetiology of the tubal damage and hydrosalpinges could have an impact on early pregnancy outcomes. It is conceivable that a blockage caused by a physical process such as adhesions or endometriosis could impact early pregnancy outcomes only via the mechanical mechanisms proposed by Eytan 2001, Mansour 1991, Shahara 1999 and Lu 2013 (97–100). Whereas, an infective process such as pelvic inflammatory disease could mean that the mechanisms proposed by Mukherjee 1996 are also at play (101).

Similarly, the disease progression from a healthy fallopian tube to a grossly distended, blocked, hydrosalpingic tube is not well documented and there are no established systems for grading of severity of disease. Diagnosis tends to be either present or absent. In reality there will be a progression of the disease from health to severely damaged. As the entire role of the fallopian tube with regards pregnancy is not known, and the aetiology behind the negative impactive of hydrosalpinges and blocked tubes on pregnancy is not known, it is not possible to state at which point or severity of damage the negative impact begins. It is logical to say, however, that early in the disease process, at which point there is some but not total disruption to the function and patency of the tubes, and therefore the hydrosalpingic appearances are not present, the earlier proposed mechanisms by which hydrosalpinges may have a negative impact on pregnancy outcomes, may start to have their impact, whether that be by mechanical impedance or altering of the endometrial receptivity or altering the immunological response to pregnancy or altered flow of fluid and debris in the cavity.

Ultimately until it is established exactly why tubal blockage and hydrosalpinges have a negative impact on fertility and other early pregnancy outcomes, it is not possible to establish if different aetiologies for tubal damage affect pregnancies in different ways.

Discussion over tubal pathology is not recommended by the RCOG or ESHRE in their respective guidelines and this chapter and the previous one provides evidence that this should be considered when these professional bodies update their respective guidance (5,7). These

results further reinforce the evidence from chapter two that tubal pathology is a risk factor for miscarriage and therefore should be screened for in women with recurrent losses especially where no other causes such as APS, endocrine or anatomical issues are detected. And should they be found; women should be counselled as to their negative impact for both pregnancy rates and pregnancy loss rates.

The reasons for the lack of differences between pregnancy outcomes for the two blocked tubes subgroup analysis compared to the one blocked tubes subgroup analysis and the positive pregnancy tests in women with apparently two blocked tubes are unclear but could indicate issues with the HyCoSy itself. It is possible that the women with two blocked tubes on HyCoSy had false positives due to difficulties with the scan caused by individual patient factors or technical factors as discussed earlier. HyCoSy and indeed HSG are considered screening tests for tubal blockage. Their sensitivity and specificity have been discussed previously so there may be false positives. Accuracy of these tests also depends upon the previously discussed patient factors and operator factors and there will also have been a learning curve in terms of operator skill. Tubal function, as previously discussed, does not rely solely on tubal patency and it may be that the other components of tubal function in these cases allowed the woman to get pregnant. Furthermore, as a muscular tube, fallopian tubes are liable to spasm causing temporary blockage which could would be detected at HyCoSy as the HyCoSy only tests for patency at a specific moment. The interplay of all of the above factors, could therefore explain why women with two apparently blocked tubes could fall pregnant.

The best method to treat such women has not been established and so further high-quality randomised trial evidence is required to establish this. However, as evidenced by the results from the intervention part of chapter two, a cautious discussion could be had over the potential benefits of tubal surgery to reduce these risks. It would seem logical that using HyCoSy to detect tubal pathology would be the best method. This is for the same reasons that it was used in this study as outlined in chapter one when the methods for detection of tubal pathology were discussed. Further research could also consider the feasibility of HyCoSy use in this population due to the difficulties we faced in performing HyCoSys in all the women that we had originally recruited. Therefore, perhaps it would be better for HyCoSys to be considered as a second line investigation, in those women for whom routine investigations did not establish a potential cause.

Conclusion

Over one third of the recurrent miscarriage population may have blocked fallopian tubes and around 6% may have hydrosalpinx. These women should be counselled that their tubal pathology may reduce their chances of falling pregnancy, significantly increase their risk of a further pregnancy loss and reduce their chances of a live birth beyond 24 weeks of gestation. Professional bodies should update their guidance to reflect this new evidence.

CHAPTER FOUR:

METHODS FOR MANAGEING MISCARRIAGE: A NETWORK META-ANALYSIS

Authors and contributions:

Dr Jayasish Ghosh designed the data extraction form, acted as first reviewer for study selection, data extraction, quality assessment, performed the paired wise meta-analysis, GRADEd the evidence, prepared the manuscript, figures and tables.

Dr Arygro Papadopoulou acted as a third reviewer and checked all data extraction and quality assessment, performed GRADEing of evidence and helped to prepare the summary of findings tables.

Dr Adam Devall is the corresponding author and acted as a second reviewer for study selection, data extraction and quality assessment and edited and revised the manuscript.

Dr Hannah Jeffery acted as a second reviewer for study selection, data extraction and quality assessment.

Miss Leanne Beeson acted as a second reviewer for study selection, data extraction and quality assessment.

Dr Vivian Do acted as a second reviewer for study selection, data extraction and quality assessment

Dr Malcolm Price advised on the network meta-analysis and provided comments on the manuscript

Dr Aurelio Tobias performed the network meta-analysis

Dr Özge Tunçalp helped to design the network meta-analysis and provided comments on the manuscript

Dr Antonella Lavelanet provided comments on the manuscript

Dr A Metin Gülmezoglu helped to design the network meta-analysis and provided comments on the manuscript

Prof Arri Coomarasamy co-conceived the concept, helped to design the network meta-analysis and edited and revised the manuscript.

Dr Ioannis D Gallos co-conceived the concept, helped to design the network meta-analysis, acted as the final decision maker over author disagreements, helped with GRADEing of evidence and preparation of summary of findings tables and edited and revised the manuscript.

Preamble

After our initial introduction where we discussed the background to miscarriage, we went on to discuss new evidence that fallopian tube pathology, whether the tubes are blocked or a hydrosalpinx has formed, and its negative impact on key reproductive outcomes in chapters two and three. In chapter four we will be discussing the care of women who have already miscarried and require management.

Abstract

Background

Miscarriage, defined as the spontaneous loss of a pregnancy before 24 weeks' gestation, is common with approximately 25% of women experiencing a miscarriage in their lifetime. An estimated 15% of pregnancies end in miscarriage. Miscarriage can lead to serious morbidity, including haemorrhage, infection, and even death, particularly in settings without adequate healthcare provision. Early miscarriages occur during the first 14 weeks of pregnancy, and can be managed expectantly, medically or surgically. However, there is uncertainty about the relative effectiveness and risks of each option.

Objectives

To estimate the relative effectiveness and safety profiles for the different management methods for early miscarriage, and to provide rankings of the available methods according to their effectiveness, safety, and side-effect profile using a network meta-analysis.

Search methods

We searched the Cochrane Pregnancy and Childbirth's Trials Register (9 February 2021), ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (12 February 2021), and reference lists of retrieved studies.

Selection criteria

We included all randomised controlled trials assessing the effectiveness or safety of methods for miscarriage management. Early miscarriage was defined as less than or equal to 14 weeks of gestation, and included missed and incomplete miscarriage. Management of late miscarriages after 14 weeks of gestation (often referred to as intrauterine fetal deaths) was not eligible for inclusion in the review. Cluster- and quasi-randomised trials were eligible for inclusion. Randomised trials published only as abstracts were eligible if sufficient information could be retrieved. We excluded non-randomised trials.

Data collection and analysis

At least three review authors independently assessed the trials for inclusion and risk of bias, extracted data and checked them for accuracy. We estimated the relative effects and rankings for the primary outcomes of complete miscarriage and composite outcome of death or serious complications. The certainty of evidence was assessed using GRADE. Relative effects for the primary outcomes are reported subgrouped by the type of miscarriage (incomplete and

missed miscarriage). We also performed pairwise meta-analyses and network meta-analysis to determine the relative effects and rankings of all available methods.

Main results

Our network meta-analysis included 78 randomised trials involving 17,795 women from 37 countries. Most trials (71/78) were conducted in hospital settings and included women with missed or incomplete miscarriage. Across 158 trial arms, the following methods were used: 51 trial arms (33%) used misoprostol; 50 (32%) used suction aspiration; 26 (16%) used expectant management or placebo; 17 (11%) used dilatation and curettage; 11 (6%) used mifepristone plus misoprostol; and three (2%) used suction aspiration plus cervical preparation. Of these 78 studies, 71 (90%) contributed data in a usable form for meta-analysis.

Complete miscarriage

Based on the relative effects from the network meta-analysis of 59 trials (12,591 women), we found that five methods may be more effective than expectant management or placebo for achieving a complete miscarriage:

- Suction aspiration after cervical preparation (risk ratio (RR) 2.12, 95% confidence interval (CI) 1.41 to 3.20, low-certainty evidence),
- Dilatation and curettage (RR 1.49, 95% CI 1.26 to 1.75, low-certainty evidence),
- Suction aspiration (RR 1.44, 95% CI 1.29 to 1.62, low-certainty evidence),
- Mifepristone plus misoprostol (RR 1.42, 95% CI 1.22 to 1.66, moderate-certainty evidence),

- Misoprostol (RR 1.30, 95% CI 1.16 to 1.46, low-certainty evidence).

The highest ranked surgical method was suction aspiration after cervical preparation. The highest ranked non-surgical treatment was mifepristone plus misoprostol. All surgical methods were ranked higher than medical methods, which in turn ranked above expectant management or placebo.

Composite outcome of death and serious complications

Based on the relative effects from the network meta-analysis of 35 trials (8161 women), we found that four methods with available data were compatible with a wide range of treatment effects compared with expectant management or placebo:

- Dilatation and curettage (RR 0.43, 95% CI 0.17 to 1.06, low-certainty evidence),
- Suction aspiration (RR 0.55, 95% CI 0.23 to 1.32, low-certainty evidence)
- Misoprostol (RR 0.50, 95% CI 0.22 to 1.15, low-certainty evidence),
- Mifepristone plus misoprostol (RR 0.76, 95% CI 0.31 to 1.84, low-certainty evidence).

Importantly, no deaths were reported in these studies, thus this composite outcome was entirely composed of serious complications, including blood transfusions, uterine perforations, hysterectomies, and intensive care unit admissions. Expectant management and placebo ranked the lowest when compared with alternative treatment interventions.

Subgroup analyses by type of miscarriage (missed or incomplete) agreed with the overall analysis in that surgical methods were the most effective treatment, followed by medical

methods and then expectant management or placebo, but there are possible subgroup differences in the effectiveness of the available methods.

Authors' conclusions

Based on relative effects from the network meta-analysis, all surgical and medical methods for managing a miscarriage may be more effective than expectant management or placebo. Surgical methods were ranked highest for managing a miscarriage, followed by medical methods, which in turn ranked above expectant management or placebo. Expectant management or placebo had the highest chance of serious complications, including the need for unplanned or emergency surgery. A subgroup analysis showed that surgical and medical methods may be more beneficial in women with missed miscarriage compared to women with incomplete miscarriage. Since type of miscarriage (missed and incomplete) appears to be a source of inconsistency and heterogeneity within these data, we acknowledge that the main network meta-analysis may be unreliable. However, we plan to explore this further in future updates and consider the primary analysis as separate networks for missed and incomplete miscarriage.

The manuscript that follows this page has been published by *Cochrane.*

Publication 2: Ghosh J, Papadopoulou A, Devall AJ, Jeffery HC, Beeson LE, Do V, Price MJ, Tobias A, Tunçalp Ö, Lavelanet A, Gülmezoglu AM, Coomarasamy A, Gallos ID. **Methods for managing miscarriage: a network meta-analysis**. Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD012602. DOI: 10.1002/14651858.CD012602.pub2.

Page 125: Start of publication

Manuscript

Cochrane Library

Cochrane Database of Systematic Reviews

Methods for managing miscarriage: a network meta-analysis (Review)

Ghosh J, Papadopoulou A, Devall AJ, Jeffery HC, Beeson LE, Do V, Price MJ, Tobias A, Tunçalp Ö, Lavelanet A, Gülmezoglu AM, Coomarasamy A, Gallos ID

Ghosh J, Papadopoulou A, Devall AJ, Jeffery HC, Beeson LE, Do V, Price MJ, Tobias A, Tunçalp Ö, Lavelanet A, Gülmezoglu AM, Coomarasamy A, Gallos ID.
Methods for managing miscarriage: a network meta-analysis.
Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD012602.
DOI: 10.1002/14651858.CD012602.pub2.

www.cochranelibrary.com

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 17
OBJECTIVES 17
METHODS 17
Figure 1. 20
RESULTS 25
Figure 2. 26
Figure 3. 27
Figure 4. 31
Figure 5. 32
Figure 6. 33
Figure 7. 35
Figure 8. 36
Figure 9. 37
Figure 10. 38
Figure 11. 39
Figure 12. 40
Figure 13. 41
Figure 14. 42
Figure 15. 43
Figure 16. 44
Figure 17. 45
Figure 18. 46
Figure 19. 47
Figure 20. 48
Figure 21. 49
Figure 22. 50
Figure 23. 51
Figure 24. 52
Figure 25. 54
Figure 26. 55
Figure 27. 56
Figure 28. 57
Figure 29. 58
Figure 30. 59
Figure 31. 60
Figure 32. 61
Figure 33. 62
Figure 34. 63
Figure 35. 64
Figure 36. 65
Figure 37. 66
Figure 38. 67
Figure 39. 68
Figure 40. 70
Figure 41. 71
Figure 42. 72
Figure 43. 73

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 44. 74
Figure 45. 75
Figure 46. 76
Figure 47. 77
Figure 48. 78
Figure 49. 79
Figure 50. 81
Figure 51. 82
DISCUSSION 83
AUTHORS' CONCLUSIONS 85
ACKNOWLEDGEMENTS 85
REFERENCES 87
CHARACTERISTICS OF STUDIES 110
DATA AND ANALYSES 192
Analysis 1.1. Comparison 1: Suction aspiration vs Misoprostol, Outcome 1: Complete Miscarriage 194
Analysis 1.2. Comparison 1: Suction aspiration vs Misoprostol, Outcome 2: Composite outcome of death or serious complication 195
Analysis 1.3. Comparison 1: Suction aspiration vs Misoprostol, Outcome 3: Need for unplanned/emergency surgical procedure 195
Analysis 1.4. Comparison 1: Suction aspiration vs Misoprostol, Outcome 4: Pain score 196
Analysis 1.5. Comparison 1: Suction aspiration vs Misoprostol, Outcome 5: Pelvic inflammatory disease, sepsis or endometritis 196
Analysis 1.6. Comparison 1: Suction aspiration vs Misoprostol, Outcome 6: Change in haemoglobin measurements before and after the miscarriage 197
Analysis 1.7. Comparison 1: Suction aspiration vs Misoprostol, Outcome 7: Days of bleeding 197
Analysis 1.8. Comparison 1: Suction aspiration vs Misoprostol, Outcome 8: Cervical tear 197
Analysis 1.9. Comparison 1: Suction aspiration vs Misoprostol, Outcome 9: Mean duration of hospital stay (days) 198
Analysis 1.10. Comparison 1: Suction aspiration vs Misoprostol, Outcome 10: Re-admission to hospital 198
Analysis 1.11. Comparison 1: Suction aspiration vs Misoprostol, Outcome 11: Nausea 198
Analysis 1.12. Comparison 1: Suction aspiration vs Misoprostol, Outcome 12: Vomiting 199
Analysis 1.13. Comparison 1: Suction aspiration vs Misoprostol, Outcome 13: Diarrhoea 199
Analysis 1.14. Comparison 1: Suction aspiration vs Misoprostol, Outcome 14: Pyrexia 200
Analysis 1.15. Comparison 1: Suction aspiration vs Misoprostol, Outcome 15: Anxiety score 200
Analysis 1.16. Comparison 1: Suction aspiration vs Misoprostol, Outcome 16: Depression score 200
Analysis 2.1. Comparison 2: Suction aspiration vs Mifepristone + Misoprostol, Outcome 1: Complete Miscarriage 201
Analysis 2.2. Comparison 2: Suction aspiration vs Mifepristone + Misoprostol, Outcome 2: Composite outcome of death or serious complication 202
Analysis 2.3. Comparison 2: Suction aspiration vs Mifepristone + Misoprostol, Outcome 3: Need for unplanned/emergency surgical procedure 202
Analysis 2.4. Comparison 2: Suction aspiration vs Mifepristone + Misoprostol, Outcome 4: Pelvic inflammatory disease, sepsis or endometritis 202
Analysis 2.5. Comparison 2: Suction aspiration vs Mifepristone + Misoprostol, Outcome 5: Re-admission to hospital 202
Analysis 3.1. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 1: Complete Miscarriage 204
Analysis 3.2. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 2: Composite outcome of death or serious complication 204
Analysis 3.3. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 3: Need for unplanned/emergency surgical procedure 204
Analysis 3.4. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 4: Pelvic inflammatory disease, sepsis or endometritis 205
Analysis 3.5. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 5: Mean volumes of blood loss (millilitres) .. 205
Analysis 3.6. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 6: Change in haemoglobin measurements before and after the miscarriage 205
Analysis 3.7. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 7: Days of bleeding 205
Analysis 3.8. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 8: Cervical tear 206
Analysis 3.9. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 9: Mean duration of hospital stay (days) 206

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 3.10. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 10: Re-admission to hospital 206
Analysis 3.11. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 11: Vomiting 206
Analysis 3.12. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 12: Pyrexia 207
Analysis 4.1. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 1: Complete Miscarriage 208
Analysis 4.2. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 2: Composite outcome of death or serious complication 209
Analysis 4.3. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 3: Need for unplanned/emergency surgical procedure 209
Analysis 4.4. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 4: Pelvic inflammatory disease, sepsis or endometritis 209
Analysis 4.5. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 5: Mean volumes of blood loss (millilitres) 210
Analysis 4.6. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 6: Change in haemoglobin measurements before and after the miscarriage 210
Analysis 4.7. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 7: Days of bleeding 210
Analysis 4.8. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 8: Cervical tear 210
Analysis 4.9. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 9: Mean duration of hospital stay (days) 211
Analysis 4.10. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 10: Re-admission to hospital 211
Analysis 4.11. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 11: Vomiting 211
Analysis 4.12. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 12: Diarrhoea 211
Analysis 4.13. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 13: Pyrexia 212
Analysis 4.14. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 14: Anxiety score 212
Analysis 4.15. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 15: Depression score 212
Analysis 5.1. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 1: Complete Miscarriage 213
Analysis 5.2. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 2: Composite outcome of death or serious complication 213
Analysis 5.3. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 3: Need for unplanned/emergency surgical procedure 214
Analysis 5.4. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 4: Pelvic inflammatory disease, sepsis or endometritis 214
Analysis 5.5. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 5: Change in haemoglobin measurements before and after the miscarriage 214
Analysis 5.6. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 6: Days of bleeding 214
Analysis 5.7. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 7: Re-admission to hospital 215
Analysis 5.8. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 8: Nausea 215
Analysis 5.9. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 9: Vomiting 215
Analysis 5.10. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 10: Diarrhoea 215
Analysis 5.11. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 11: Pyrexia 216
Analysis 6.1. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 1: Complete Miscarriage 217
Analysis 6.2. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 2: Composite outcome of death or serious complication 217
Analysis 6.3. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 3: Need for unplanned/emergency surgical procedure 218
Analysis 6.4. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 4: Pain score 218
Analysis 6.5. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 5: Pelvic inflammatory disease, sepsis or endometritis 218
Analysis 6.6. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 6: Mean volumes of blood loss (millilitres) 218
Analysis 6.7. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 7: Days of bleeding 219
Analysis 6.8. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 8: Cervical tear 219
Analysis 6.9. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 9: Re-admission to hospital 219
Analysis 6.10. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 10: Vomiting 219
Analysis 6.11. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 11: Nausea 220
Analysis 6.12. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 12: Diarrhoea 220
Analysis 6.13. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 13: Depression score 220
Analysis 7.1. Comparison 7: Misoprostol vs Suction aspiration + Cervical preparation, Outcome 1: Complete Miscarriage 221

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 7.2. Comparison 7: Misoprostol vs Suction aspiration + Cervical preparation, Outcome 2: Pyrexia 221
Analysis 8.1. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 1: Complete Miscarriage 222
Analysis 8.2. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 2: Composite outcome of death or serious complication 223
Analysis 8.3. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 3: Need for unplanned/emergency surgical procedure 223
Analysis 8.4. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 4: Pain score 223
Analysis 8.5. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 5: Pelvic inflammatory disease, sepsis or endometritis 224
Analysis 8.6. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 6: Change in haemoglobin measurements before and after the miscarriage 224
Analysis 8.7. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 7: Days of bleeding 224
Analysis 8.8. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 8: Mean duration of hospital stay (days) 224
Analysis 8.9. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 9: Re-admission to hospital 225
Analysis 8.10. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 10: Nausea 225
Analysis 8.11. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 11: Vomiting 225
Analysis 8.12. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 12: Diarrhoea 226
Analysis 8.13. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 13: Pyrexia 226
Analysis 8.14. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 14: Anxiety score 226
Analysis 8.15. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 15: Depression score 226
Analysis 9.1. Comparison 9: Dilatation & Curettage vs Expectant/ Placebo, Outcome 1: Complete Miscarriage 227
Analysis 9.2. Comparison 9: Dilatation & Curettage vs Expectant/ Placebo, Outcome 2: Pelvic inflammatory disease, sepsis or endometritis 227
Analysis 9.3. Comparison 9: Dilatation & Curettage vs Expectant/ Placebo, Outcome 3: Days of bleeding 227
Analysis 10.1. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 1: Complete Miscarriage 228
Analysis 10.2. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 2: Composite outcome of death or serious complication 229
Analysis 10.3. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 3: Need for unplanned/emergency surgical procedure 229
Analysis 10.4. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 4: Pain score 229
Analysis 10.5. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 5: Pelvic inflammatory disease, sepsis or endometritis 229
Analysis 10.6. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 6: Days of bleeding 230
Analysis 10.7. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 7: Pyrexia 230
APPENDICES 230
HISTORY 231
CONTRIBUTIONS OF AUTHORS 231
DECLARATIONS OF INTEREST 231
SOURCES OF SUPPORT 232
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 232
INDEX TERMS 233

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Methods for managing miscarriage: a network meta-analysis

Jay Ghosh[1], Argyro Papadopoulou[1], Adam J Devall[1], Hannah C Jeffery[1], Leanne E Beeson[2], Vivian Do[3], Malcolm J Price[4], Aurelio Tobias[1], Özge Tunçalp[5], Antonella Lavelanet[5], Ahmet Metin Gülmezoglu[6], Arri Coomarasamy[1], Ioannis D Gallos[1]

[1]Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research (IMSR), WHO Collaborating Centre for Global Women's Health Research, University of Birmingham, Birmingham, UK. [2]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK. [3]University of Birmingham, Birmingham, UK. [4]Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, UK. [5]UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Sexual and Reproductive Health and Research, World Health Organization, Geneva, Switzerland. [6]Concept Foundation, Geneva, Switzerland

Contact address: Adam J Devall,

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New, published in Issue 6, 2021.

Citation: Ghosh J, Papadopoulou A, Devall AJ, Jeffery HC, Beeson LE, Do V, Price MJ, Tobias A, Tunçalp Ö, Lavelanet A, Gülmezoglu AM, Coomarasamy A, Gallos ID. Methods for managing miscarriage: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2021, Issue 6. Art. No.: CD012602. DOI: 10.1002/14651858.CD012602.pub2.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Miscarriage, defined as the spontaneous loss of a pregnancy before 24 weeks' gestation, is common with approximately 25% of women experiencing a miscarriage in their lifetime. An estimated 15% of pregnancies end in miscarriage. Miscarriage can lead to serious morbidity, including haemorrhage, infection, and even death, particularly in settings without adequate healthcare provision. Early miscarriages occur during the first 14 weeks of pregnancy, and can be managed expectantly, medically or surgically. However, there is uncertainty about the relative effectiveness and risks of each option.

Objectives

To estimate the relative effectiveness and safety profiles for the different management methods for early miscarriage, and to provide rankings of the available methods according to their effectiveness, safety, and side-effect profile using a network meta-analysis.

Search methods

We searched the Cochrane Pregnancy and Childbirth's Trials Register (9 February 2021), ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (12 February 2021), and reference lists of retrieved studies.

Selection criteria

We included all randomised controlled trials assessing the effectiveness or safety of methods for miscarriage management. Early miscarriage was defined as less than or equal to 14 weeks of gestation, and included missed and incomplete miscarriage. Management of late miscarriages after 14 weeks of gestation (often referred to as intrauterine fetal deaths) was not eligible for inclusion in the review. Cluster- and quasi-randomised trials were eligible for inclusion. Randomised trials published only as abstracts were eligible if sufficient information could be retrieved. We excluded non-randomised trials.

Data collection and analysis

At least three review authors independently assessed the trials for inclusion and risk of bias, extracted data and checked them for accuracy. We estimated the relative effects and rankings for the primary outcomes of complete miscarriage and composite outcome of death or serious complications. The certainty of evidence was assessed using GRADE. Relative effects for the primary outcomes are reported

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

subgrouped by the type of miscarriage (incomplete and missed miscarriage). We also performed pairwise meta-analyses and network meta-analysis to determine the relative effects and rankings of all available methods.

Main results

Our network meta-analysis included 78 randomised trials involving 17,795 women from 37 countries. Most trials (71/78) were conducted in hospital settings and included women with missed or incomplete miscarriage. Across 158 trial arms, the following methods were used: 51 trial arms (33%) used misoprostol; 50 (32%) used suction aspiration; 26 (16%) used expectant management or placebo; 17 (11%) used dilatation and curettage; 11 (6%) used mifepristone plus misoprostol; and three (2%) used suction aspiration plus cervical preparation. Of these 78 studies, 71 (90%) contributed data in a usable form for meta-analysis.

Complete miscarriage

Based on the relative effects from the network meta-analysis of 59 trials (12,591 women), we found that five methods may be more effective than expectant management or placebo for achieving a complete miscarriage:

· suction aspiration after cervical preparation (risk ratio (RR) 2.12, 95% confidence interval (CI) 1.41 to 3.20, low-certainty evidence),

· dilatation and curettage (RR 1.49, 95% CI 1.26 to 1.75, low-certainty evidence),

· suction aspiration (RR 1.44, 95% CI 1.29 to 1.62, low-certainty evidence),

· mifepristone plus misoprostol (RR 1.42, 95% CI 1.22 to 1.66, moderate-certainty evidence),

· misoprostol (RR 1.30, 95% CI 1.16 to 1.46, low-certainty evidence).

The highest ranked surgical method was suction aspiration after cervical preparation. The highest ranked non-surgical treatment was mifepristone plus misoprostol. All surgical methods were ranked higher than medical methods, which in turn ranked above expectant management or placebo.

Composite outcome of death and serious complications

Based on the relative effects from the network meta-analysis of 35 trials (8161 women), we found that four methods with available data were compatible with a wide range of treatment effects compared with expectant management or placebo:

· dilatation and curettage (RR 0.43, 95% CI 0.17 to 1.06, low-certainty evidence),

· suction aspiration (RR 0.55, 95% CI 0.23 to 1.32, low-certainty evidence),

· misoprostol (RR 0.50, 95% CI 0.22 to 1.15, low-certainty evidence),

· mifepristone plus misoprostol (RR 0.76, 95% CI 0.31 to 1.84, low-certainty evidence).

Importantly, no deaths were reported in these studies, thus this composite outcome was entirely composed of serious complications, including blood transfusions, uterine perforations, hysterectomies, and intensive care unit admissions. Expectant management and placebo ranked the lowest when compared with alternative treatment interventions.

Subgroup analyses by type of miscarriage (missed or incomplete) agreed with the overall analysis in that surgical methods were the most effective treatment, followed by medical methods and then expectant management or placebo, but there are possible subgroup differences in the effectiveness of the available methods.

Authors' conclusions

Based on relative effects from the network meta-analysis, all surgical and medical methods for managing a miscarriage may be more effective than expectant management or placebo. Surgical methods were ranked highest for managing a miscarriage, followed by medical methods, which in turn ranked above expectant management or placebo. Expectant management or placebo had the highest chance of serious complications, including the need for unplanned or emergency surgery. A subgroup analysis showed that surgical and medical methods may be more beneficial in women with missed miscarriage compared to women with incomplete miscarriage. Since type of miscarriage (missed and incomplete) appears to be a source of inconsistency and heterogeneity within these data, we acknowledge that the main network meta-analysis may be unreliable. However, we plan to explore this further in future updates and consider the primary analysis as separate networks for missed and incomplete miscarriage.

PLAIN LANGUAGE SUMMARY

Which management option is best when women experience an early miscarriage?

What is the issue?

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Miscarriage is the most common cause of pregnancy loss and one of the most common complications in early pregnancy. An estimated 15% of pregnancies will end in miscarriage, with 25% of women experiencing a miscarriage in their lifetime. Miscarriage can lead to serious complications, including haemorrhage and infection, and even death, particularly in low-income countries. Miscarriage is generally defined as the spontaneous loss of a pregnancy before 24 weeks' gestation. Most miscarriages happen in the first 14 weeks, and are known as early miscarriages.

Why is this important?

Miscarriage can be managed expectantly (waiting for the pregnancy tissue to pass naturally), medically (tablets given to make the womb expel the pregnancy tissue) or surgically (removal of the pregnancy tissue during surgery). However, there is uncertainty about the effectiveness, safety, and side effects of the available methods for managing a miscarriage. The aim of this Cochrane Review is to find out which method is the most effective and safest with the least side effects. We collected and analysed all the relevant studies to answer this question.

What evidence did we find?

We searched for evidence in February 2021 and identified 78 studies involving 17,795 women. Most women were managed in hospitals. Women were diagnosed with missed (also called silent miscarriage where no pregnancy tissue has been expelled and there is no bleeding or pain) or incomplete miscarriage (already started to bleed or have pain and perhaps expelled some pregnancy tissue). We found evidence for six different methods of managing a miscarriage; three surgical methods (suction aspiration plus cervical preparation, dilatation and curettage, or suction aspiration), two medical methods (mifepristone plus misoprostol or misoprostol alone), and expectant management or placebo.

The analysis suggested that all three surgical methods and both medical methods may be more effective than expectant management or placebo for completing the process of miscarriage. Suction aspiration plus cervical preparation was the best method of miscarriage management followed by dilatation and curettage, and suction aspiration alone. The two medical methods of mifepristone combined with misoprostol, and misoprostol alone were ranked fourth and fifth best methods, respectively.

From the available data, we cannot learn much for the outcome of death or serious complications. No deaths were reported in the studies that contributed towards this outcome. Amongst the serious complications, the majority were women who required blood transfusions, some had womb perforations related to surgery or required further life-saving procedures. We could not know which method is best for this outcome due to limited data. However, expectant management or placebo was associated with more serious complications compared with the alternative treatment options.

We also looked separately at women suffering from an incomplete miscarriage compared to those suffering from a missed miscarriage. For both groups of women, all three surgical methods and both medical methods were found to be more effective than expectant management or placebo for providing a definitive treatment for a miscarriage. These analyses for incomplete and missed miscarriages agreed with the overall analysis in that surgical methods were better for providing a definitive treatment for a miscarriage than medical methods, which in turn were better than expectant management or placebo. However, the benefits for women with missed miscarriages undergoing any management method other than expectant management or placebo were far greater compared to women with incomplete miscarriages. This is probably because expectant management or placebo is more effective in women in whom the process of miscarriage has already started compared with women in whom the process is yet to start.

What does this mean?

All methods were generally more effective for managing a miscarriage compared with expectant management or placebo, but surgical methods were more effective than medical methods. Expectant management or placebo has the lowest chance of successfully treating a miscarriage and has the highest chance of serious complications and the need for unplanned or emergency surgery. In this review we found that the benefits for women with missed miscarriages undergoing any management method other than expectant management or placebo were far greater compared to women with incomplete miscarriages.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

SUMMARY OF FINDINGS

Summary of findings 1. Complete miscarriage

Medical and surgical management compared with expectant management or placebo for treating missed early miscarriage

Patient or population: women with missed miscarriage at ≤14 weeks gestation

Settings: hospital or other healthcare facility

Intervention: multiple interventions (suction aspiration, misoprostol, dilation and curettage, mifepristone plus misoprostol, suction aspiration plus cervical preparation)

Comparison (reference): expectant management or placebo

Outcome: complete miscarriage

Intervention	Network evidence		Direct evidence		Indirect evidence		Illustrative comparative risks* (95% CI) for NMA estimate		
	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Risk with standard care	Risk with intervention	Risk difference with intervention
Suction aspiration plus cervical preparation	2.12 (1.41 to 3.20)	⊕⊕⊖⊖ LOW[a]	Not reported by included studies	-	2.12 (1.41 to 3.20)	⊕⊕⊖⊖ LOW[b]	640 per 1000	1000 per 1000	360 more per 1,000 (from 182 more to 577 more)
Suction aspiration	1.44 (1.29 to 1.62)	⊕⊕⊖⊖ LOW[c]	1.27 (1.08 to 1.48)	⊕⊕⊕⊖ MODERATE[d]	1.72 (1.44 to 2.06)	⊕⊕⊕⊖ MODERATE[f]	640 per 1000	922 per 1000	282 more per 1,000 (from 186 more to 397 more)
Dilation and curettage	1.49 (1.26 to 1.75)	⊕⊕⊖⊖ LOW[c]	1.25 (1.12 to 1.39)	⊕⊕⊕⊖ MODERATE[e]	1.55 (1.29 to 1.86)	⊕⊕⊖⊖ LOW[b]	640 per 1000	954 per 1000	314 more per 1,000 (from 166 more to 480 more)
Mifepristone plus misoprostol	1.42 (1.22 to 1.66)	⊕⊕⊕⊖ MODERATE[g]	1.59 (1.01 to 2.51)	⊕⊕⊕⊖ MODERATE[d]	1.40 (1.16 to 1.70)	⊕⊕⊕⊖ MODERATE[f]	640 per 1000	909 per 1000	269 more per 1,000 (from 141 more to 422 more)
Misoprostol	1.30 (1.16 to 1.46)	⊕⊕⊖⊖	1.85 (1.35 to 2.55)	⊕⊕⊕⊖	1.14 (0.99 to 1.31)	⊕⊕⊕⊖	640 per 1000	832 per 1000	192 more per 1,000 (from 102 more to 294 more)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

	LOW[c]	MODERATE[d]	MODERATE[f]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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 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] Network evidence downgraded -2 due to low certainty indirect evidence (no intransitivity, incoherence, or imprecision)
[b] Indirect evidence downgraded -2 due to limitations in study design
[c] Network evidence downgraded -2 due to moderate certainty direct evidence and incoherence between direct and indirect estimates (no intransitivity, or imprecision)
[d] Direct evidence downgraded -1 due to severe unexplained statistical heterogeneity
[e] Direct evidence downgraded -1 due to serious imprecision
[f] Indirect evidence downgraded -1 due to severe unexplained statistical heterogeneity
[g] Network evidence downgraded -1 due to moderate certainty indirect evidence (no intransitivity, incoherence, or imprecision)

Summary of findings 2. Complete miscarriage (missed miscarriage subgroup)

Medical and surgical management compared with expectant management or placebo for treating missed early miscarriage

Patient or population: women with missed miscarriage at ≤14 weeks gestation

Settings: hospital or other healthcare facility

Intervention: multiple interventions (suction aspiration, misoprostol, dilation and curettage, mifepristone plus misoprostol, suction aspiration plus cervical preparation)

Comparison (reference): expectant management or placebo

Outcome: complete miscarriage

Intervention	Network evidence		Direct evidence		Indirect evidence		Illustrative comparative risks* (95% CI) for NMA estimate		
	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Risk with standard care	Risk with intervention	Risk difference with intervention

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
Cochrane Database of Systematic Reviews

Suction aspiration plus cervical preparation	Not estimable	-	Not reported by included studies	-	Not estimable	-	Not estimable	Not estimable	Not estimable
Suction aspiration	2.43 (1.69 to 3.49)	⊕⊕⊕⊖ MODERATE[b]	1.88 (1.68 to 2.12)	⊕⊕⊕⊕ HIGH	3.35 (1.94 to 5.81)	⊕⊖⊖⊖ VERY LOW[a]	455 per 1000	942 per 1000	487 more per 1000 (from 402 more to 580 more)
Dilation and curettage	2.07 (1.19 to 3.59)	⊕⊕⊕⊕ HIGH	Not reported by included studies	-	Not estimable	-	455 per 1000	1000 per 1000	545 more per 1000 (from 313 more to 847 more)
Mifepristone plus misoprostol	1.82 (1.28 to 2.58)	⊕⊕⊕⊖ MODERATE[b]	1.25 (1.09 to 1.45)	⊕⊕⊕⊕ HIGH	2.40 (1.58 to 3.65)	⊕⊕⊕⊖ MODERATE[c]	455 per 1000	828 per 1000	373 more per 1000 (from 127 more to 719 more)
Misoprostol	1.67 (1.18 to 2.37)	⊕⊕⊖⊖ LOW[e]	3.18 (1.48 to 6.85)	⊕⊕⊕⊖ MODERATE[d]	1.16 (0.81 to 1.67)	⊕⊕⊕⊖ MODERATE[c]	455 per 1000	760 per 1000	305 more per 1000 (from 82 more to 623 more)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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 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] Indirect evidence downgraded -3 due to multiple crucial limitations in study design, severe unexplained statistical heterogeneity and imprecision
[b] Network evidence downgraded -1 due to high certainty direct evidence and incoherence between direct and indirect estimates (no intransitivity, or imprecision)
[c] Indirect evidence downgraded -1 due to severe unexplained statistical heterogeneity
[d] Direct evidence downgraded -1 due to severe unexplained statistical heterogeneity
[e] Network evidence downgraded -2 due to moderate certainty indirect evidence and incoherence between direct and indirect estimates (no intransitivity, or imprecision)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Summary of findings 3. Complete miscarriage (incomplete miscarriage subgroup)

Medical and surgical management compared with expectant management or placebo for treating incomplete early miscarriage

Patient or population: women with incomplete miscarriage at ≤14 weeks gestation

Settings: hospital or other healthcare facility

Intervention: multiple interventions (suction aspiration, misoprostol, dilation and curettage, mifepristone plus misoprostol, suction aspiration plus cervical preparation)

Comparison (reference): expectant management or placebo

Outcome: complete miscarriage

Intervention	Network evidence		Direct evidence		Indirect evidence		Illustrative comparative risks* (95% CI) for NMA estimate		
	Relative effect (95% CI)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Risk with standard care	Risk with intervention	Risk difference with intervention
Suction aspiration plus cervical preparation	Not estimable	-	Not reported by included studies	-	Not estimable	-	Not estimable	Not estimable	Not estimable
Suction aspiration	1.19 (1.09 to 1.31)	⊕⊕⊕⊖ MODERATE[c]	1.20 (0.85 to 1.69)	⊕⊖⊖⊖ VERY LOW[a]	1.28 (1.11 to 1.48)	⊕⊕⊖⊖ LOW[b]	767 per 1000	913 per 1000	146 more per 1000 (from 69 more to 238 more)
Dilation and curettage	1.19 (1.08 to 1.31)	⊕⊕⊕⊖ MODERATE[f]	1.25 (1.12 to 1.39)	⊕⊕⊕⊖ MODERATE[d]	1.15 (1.02 to 1.30)	⊕⊖⊖⊖ VERY LOW[e]	767 per 1000	913 per 1000	146 more per 1000 (from 61 more to 238 more)
Mifepristone plus misoprostol	1.08 (0.87 to 1.34)	⊕⊖⊖⊖ VERY LOW[h]	1.08 (0.90 to 1.30)	⊕⊖⊖⊖ VERY LOW[g]	Not estimable	-	767 per 1000	828 per 1000	61 more per 1000 (from 100 fewer to 261 more)
Misoprostol	1.14 (1.03 to 1.25)	⊕⊕⊕⊖ MODERATE[j]	1.04 (0.70 to 1.54)	⊕⊕⊖⊖ LOW[i]	1.12 (1.02 to 1.24)	⊕⊖⊖⊖ VERY LOW[e]	767 per 1000	874 per 1000	107 more per 1000 (from 23 more to 192 more)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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 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 -3 due to multiple crucial limitations in study design, severe unexplained statistical heterogeneity and imprecision
[b] Indirect evidence downgraded -2 due to serious imprecision
[c] Network evidence downgraded -1 due to low certainty indirect evidence upgraded by 1 as it was downgraded for imprecision
[d] Direct evidence downgraded -1 due to serious imprecision
[e] Indirect evidence downgraded -3 due to multiple crucial limitations in study design, severe unexplained statistical heterogeneity and imprecision
[f] Network evidence downgraded -1 due to moderate certainty direct evidence (no intransitivity, incoherence, or imprecision)
[g] Direct evidence downgraded -3 due to multiple crucial limitations in study design and imprecision
[h] Network evidence downgraded -3 due to very low certainty direct evidence (no intransitivity, incoherence, or imprecision)
[i] Direct evidence downgraded -2 due to serious imprecision
[j] Network evidence downgraded -1 due to low certainty direct evidence upgraded by 1 as network evidence is precise

Summary of findings 4. Composite outcome of death or serious complication

Medical and surgical management compared with expectant management or placebo for treating early miscarriage

Patient or population: women with missed or incomplete miscarriage at ≤14 weeks gestation

Settings: Hospital

Intervention: multiple interventions (suction aspiration, misoprostol, dilation plus curettage, mifepristone plus misoprostol, suction aspiration plus cervical preparation)

Comparison (reference): expectant management

Outcome: composite outcome of death or serious complication

Intervention	Network evidence		Direct evidence		Indirect evidence		Illustrative comparative risks* (95% CI) for NMA estimate		
	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Risk with standard care	Risk with intervention	Risk difference with intervention

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
Cochrane Database of Systematic Reviews

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Suction aspiration plus cervical preparation	Not reported by included studies	-	Not reported by included studies	-	Not reported by included studies	-	Not estimable	Not estimable	Not estimable
Suction aspiration	0.55 (0.23 to 1.32)	⊕⊖⊖⊖ LOW[c]	0.43 (0.12 to 1.53)	⊕⊖⊖⊖ LOW[a]	0.97 (0.21 to 4.40)	⊕⊖⊖⊖ LOW[b]	19 per 1000	10 per 1000	9 fewer per 1000 (from 15 fewer to 6 more)
Dilation and curettage	0.43 (0.17 to 1.06)	⊕⊖⊖⊖ LOW[d]	Not reported by included studies	-	0.43 (0.17 to 1.06)	⊕⊖⊖⊖ LOW[b]	19 per 1000	8 per 1000	11 fewer per 1000 (from 16 fewer to 1 more)
Mifepristone plus misoprostol	0.76 (0.31 to 1.84)	⊕⊖⊖⊖ LOW[c]	0.46 (0.13 to 1.63)	⊕⊖⊖⊖ LOW[a]	1.38 (0.37 to 5.17)	⊕⊖⊖⊖ LOW[b]	19 per 1000	14 per 1000	5 fewer per 1000 (from 13 fewer to 16 more)
Misoprostol	0.50 (0.22 to 1.15)	⊕⊖⊖⊖ LOW[d]	0.96 (0.06 to 15.08)	⊕⊖⊖⊖ LOW[a]	0.35 (0.13 to 0.97)	⊕⊖⊖⊖ LOW[b]	19 per 1000	10 per 1000	9 fewer per 1000 (from 15 fewer to 3 more)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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 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 -2 due to very serious imprecision
[b] Indirect evidence downgraded -2 due to very serious imprecision
[c] Network evidence downgraded -2 due to low certainty direct evidence (no intransitivity or incoherence)
[d] Network evidence downgraded -2 due to low certainty indirect evidence (no intransitivity or incoherence)

Summary of findings 5. Need for unplanned/emergency surgical procedure

Medical and surgical management compared with expectant management or placebo for treating early miscarriage

Patient or population: women with a miscarriage at ≤14 weeks gestation

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Settings: hospital or other healthcare facility

Intervention: multiple interventions (suction aspiration, misoprostol, dilation and curettage, mifepristone plus misoprostol, suction aspiration plus cervical preparation)

Comparison (reference): expectant management or placebo

Outcome: need for unplanned/emergency surgical procedure

Intervention	Network evidence		Direct evidence		Indirect evidence		Illustrative comparative risks* (95% CI) for NMA estimate		
	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Risk with standard care	Risk with intervention	Risk difference with intervention
Suction aspiration plus cervical preparation	Not estimable	-	Not reported by included studies	-	Not estimable	-	Not estimable	Not estimable	Not estimable
Suction aspiration	0.37 (0.22 to 0.65)	⊕⊕⊕⊖ MODERATE[b]	0.51 (0.30 to 0.87)	⊕⊕⊕⊕ HIGH	0.13 (0.05 to 0.35)	⊕⊕⊖⊖ LOW[a]	120 per 1000	44 per 1000	76 fewer per 1000 (from 42 fewer to 94 fewer)
Dilation and curettage	0.80 (0.09 to 7.02)	⊕⊖⊖⊖ VERY LOW[c]	Not reported by included studies	-	Not estimable	-	120 per 1000	96 per 1000	24 fewer per 1000 (from 109 fewer to 722 more)
Mifepristone plus misoprostol	0.64 (0.33 to 1.23)	⊕⊕⊖⊖ LOW[e]	0.32 (0.11 to 0.90)	⊕⊕⊕⊖ MODERATE[d]	0.91 (0.43 to 1.93)	⊕⊕⊖⊖ LOW[a]	120 per 1000	77 per 1000	43 less per 1000 (from 80 fewer to 28 more)
Misoprostol	1.04 (0.56 to 1.95)	⊕⊕⊖⊖ LOW[g]	0.67 (0.23 to 1.95)	⊕⊕⊖⊖ LOW[f]	1.28 (0.61 to 2.66)	⊕⊕⊖⊖ LOW[a]	120 per 1000	125 per 1000	5 more per 1000 (from 53 fewer to 114 more)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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] Indirect evidence downgraded -2 due to serious imprecision
[b] Network evidence downgraded -1 due to high certainty direct evidence downgraded due to incoherence
[c] Network evidence downgraded -1 due to low certainty indirect loop further downgraded due to imprecision
[d] Direct evidence downgraded -1 due to imprecision
[e] Network evidence downgraded -1 due to moderate certainty direct evidence downgraded due to incoherence
[f] Direct evidence downgraded -2 due to serious imprecision
[g] Network evidence downgraded due to low certainty indirect evidence with imprecision but not further downgraded as indirect evidence previously downgraded for imprecision

Summary of findings 6. Pain scores (visual analogue scale)

Medical and surgical management compared with expectant management or placebo for treating early miscarriage

Patient or population: women with a miscarriage at ≤14 weeks gestation

Settings: hospital or other healthcare facility

Intervention: multiple interventions (suction aspiration, misoprostol, dilation and curettage, mifepristone plus misoprostol, suction aspiration plus cervical preparation)

Comparison (reference): expectant management or placebo

Outcome: pain scores (visual analogue scale)

Intervention	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	Risk with intervention			
Suction aspiration plus cervical preparation	The mean pain score was 0	Not reported by included studies	-	-	
Suction aspiration	The mean pain score was 0	Not reported by included studies	-	-	
Dilation and curettage	The mean pain score was 0	Not reported by included studies	-	-	
Mifepristone plus misoprostol	The pain score in the mifepristone plus misoprostol group was on average 0.14 higher (from 0.21 lower to 0.5 higher) than in the		122 (1 RCT)	⊕⊕⊖⊖ LOW [a,b]	small effect

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

	expectant management or placebo group			
Misoprostol	The pain score in the misoprostol group was on average 0.33 higher (from 0.08 lower to 0.57 higher) than in the expectant management or placebo group	262 (3 RCTs)	⊕⊕⊖⊖ LOW [a,b]	small effect

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds 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 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] -1 as patient reported outcome
[b] -1 due to imprecision

Summary of findings 7. Pelvic inflammatory disease, sepsis or endometritis

Medical and surgical management compared with expectant management or placebo for treating early miscarriage

Patient or population: women with a miscarriage at ≤14 weeks gestation

Settings: Hospital or other healthcare facility

Intervention: multiple interventions (suction aspiration, misoprostol, dilation and curettage, mifepristone plus misoprostol, suction aspiration plus cervical preparation)

Comparison (reference): expectant management or placebo

Outcome: pelvic inflammatory disease, sepsis or endometritis

Intervention	Network evidence		Direct evidence		Indirect evidence		Illustrative comparative risks* (95% CI) for NMA estimate		
	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Risk with standard care	Risk with intervention	Risk difference with intervention

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
Cochrane Database of Systematic Reviews

Suction aspiration plus cervical preparation	Not estimable	-	Not reported by included studies	-	Not estimable	-	Not estimable	Not estimable	Not estimable
Suction aspiration	1.42 (0.88 to 2.28)	⊕⊕⊕⊖ MODERATE[c]	1.35 (0.76 to 2.41)	⊕⊕⊕⊖ MODERATE[a]	1.55 (0.66 to 3.68)	⊕⊕⊖⊖ LOW[b]	36 per 1000	51 per 1000	15 more per 1000 (from 4 fewer to 46 more)
Dilation and curettage	1.85 (1.05 to 3.25)	⊕⊖⊖⊖ VERY LOW[f]	3.30 (0.82 to 13.28)	⊕⊕⊖⊖ LOW[d]	1.65 (0.89 to 3.06)	⊕⊖⊖⊖ VERY LOW[e]	36 per 1000	67 per 1000	31 more 1000 (from 2 more to 81 more)
Mifepristone plus misoprostol	0.90 (0.48 to 1.68)	⊕⊕⊖⊖ LOW[g]	0.73 (0.30 to 1.80)	⊕⊕⊖⊖ LOW[d]	1.11 (0.47 to 2.64)	⊕⊕⊖⊖ LOW[b]	36 per 1000	32 per 1000	4 fewer per 1000 (from 19 fewer- to 25 more)
Misoprostol	1.08 (0.62 to 1.88)	⊕⊕⊕⊖ MODERATE[c]	1.84 (0.35 to 9.68)	⊕⊕⊖⊖ LOW[d]	1.10 (0.56 to 2.16)	⊕⊕⊕⊖ MODERATE[h]	36 per 1000	39 per 1000	3 more per 1000 (from 14 fewer to 32 more)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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 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 -1 due to imprecision
[b] Indirect evidence downgraded -2 due to serious imprecision
[c] Network evidence downgraded -1 due to moderate certainty direct evidence not further downgraded due to imprecision as direct evidence previously downgraded for imprecision
[d] Direct evidence downgraded -2 due to serious imprecision
[e] Indirect evidence downgraded -3 due to serious design limitations and imprecision in direct evidence
[f] Network evidence downgraded -3 due to very low certainty indirect evidence, further downgraded -1 for incoherence but upgraded +1 as network is precise
[g] Network evidence downgraded -2 due to low certainty direct evidence, not further downgraded due to imprecision as direct evidence previously downgraded for imprecision

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[h] Indirect evidence downgraded -1 due to imprecision in direct evidence

Summary of findings 8. Days of bleeding

Medical and surgical management compared with expectant management or placebo for treating early miscarriage

Patient or population: women with a miscarriage at ≤14 weeks gestation

Settings: hospital or other healthcare facility

Intervention: multiple interventions (suction aspiration, misoprostol, dilation and curettage, mifepristone plus misoprostol, suction aspiration plus cervical preparation)

Comparison (reference): expectant management or placebo

Outcome: days of bleeding

Intervention	Network evidence		Direct evidence		Indirect evidence		Illustrative comparative risks* (95% CI) for NMA estimate		
	Mean difference (95% CI)	Certainty of the evidence (GRADE)	Mean difference (95% CI)	Certainty of the evidence (GRADE)	Mean difference (95% CI)	Certainty of the evidence (GRADE)	Risk with standard care	Risk with intervention	Risk difference with intervention
Suction aspiration plus cervical preparation	Not estimable	-	Not reported by included studies	-	Not estimable	-	Not estimable	Not estimable	Not estimable
Suction aspiration	-2.00 (-3.01 to -0.99)	⊕⊖⊖⊖ VERY LOW[c]	-2.75 (-4.08 to -1.42)	⊕⊕⊖⊖ LOW[a]	-0.73 (-2.12 to 0.66)	⊕⊖⊖⊖ VERY LOW[b]	10 days	8 days	2 days less (from 0.99 days less to 3.01 days less)
Dilation and curettage	-1.96 (-3.48 to -0.45)	⊕⊕⊖⊖ LOW[f]	-1.26 (-2.27 to -0.25)	⊕⊕⊖⊖ LOW[d]	-2.47 (-4.47 to -0.46)	⊕⊖⊖⊖ VERY LOW[e]	10 days	8.04 days	1.96 days less (from 0.45 days less to 3.48 days less)
Mifepristone plus misoprostol	-0.14 (-1.71 to 1.43)	⊕⊖⊖⊖ VERY LOW[h]	0.70 (-0.43 to 1.83)	⊕⊖⊖⊖ VERY LOW[g]	-0.77 (-2.83 to 1.30)	⊕⊖⊖⊖ VERY LOW[b]	10 days	9.86 days	0.14 days less (from 1.71 days less to 1.43 days more)
Misoprostol	-0.47	⊕⊖⊖⊖	0.32 (-2.19 to 2.84)	⊕⊖⊖⊖ VERY LOW[i]	-0.96 (-2.27 to 0.35)	⊕⊕⊖⊖ LOW[j]	10 days	9.53 days	0.47 days less (from 1.53 days less to 0.60 days more)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(-1.53 to 0.60)	VERY LOW[k]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **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 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 -2 due to patient reported outcome and significant heterogeneity
[b] Indirect evidence downgraded -4 due to patient reported outcome, significant heterogeneity and serious imprecision
[c] Network evidence downgraded -4 due to low certainty direct evidence, further downgraded due to incoherence and not upgraded as direct grade not downgraded for imprecision
[d] Direct evidence downgraded -2 due to patient reported outcome and imprecision
[e] Indirect evidence downgraded -4 due to very low certainty direct evidence which was due to patient reported outcome, moderate design limitations and serious imprecision
[f] Network evidence downgraded -2 due to low certainty direct evidence, further downgraded -1 for incoherence but upgraded +1 as network is precise and direct evidence was previously downgraded for imprecision
[g] Direct evidence downgraded -3 due to patient reported outcome and serious imprecision
[h] Network evidence downgraded -5 due to very low certainty direct evidence, further downgraded due to incoherence but not even further downgraded due to imprecision as direct evidence previously downgraded for imprecision
[i] Direct evidence downgraded -4 due to patient reported outcome, significant heterogeneity and serious imprecision
[j] Indirect evidence downgraded -2 due to patient reported outcome and significant heterogeneity
[k] Network evidence downgraded -3 due to low certainty indirect evidence downgraded -1 due to imprecision

Summary of findings 9. Women's views/satisfaction

Medical and surgical management compared with expectant management or placebo for treating early miscarriage

Patient or population: women with a miscarriage at ≤14 weeks gestation

Settings: hospital or other healthcare facility

Intervention: multiple interventions (suction aspiration, misoprostol, dilation and curettage, mifepristone plus misoprostol, suction aspiration plus cervical preparation)

Comparison (reference): expectant management or placebo

Outcome: women's views/ satisfaction

Intervention	Narrative synthesis	№ of participants (studies)	Certainty of the evidence	Comments

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

			(GRADE)
Suction aspiration plus cervical preparation	Not reported by included studies	(0 RCTs)	-
Suction aspiration	2 trials described 92 out of 96 women (98.5%) as being satisfied with suction aspiration compared to 97 out of 99 women (98.0%) for expectant management or placebo. 1 trial used a 10 point numerical scale and found suction aspiration had a satisfaction score of 7.57 from 175 women and expectant management or placebo also had a 7.57 score from 177 women.	547 (3 RCTs)	⊕⊕⊕⊖ MODERATE[a]
Dilatation and curettage	Not reported by included studies	(0 RCTs)	-
Mifepristone plus misoprostol	1 trial used a visual analogue scale and found Mifepristone plus misoprostol had a score of 28.6 (SD 24.8) from 60 women compared to 25.2 (SD 25.6) from 62 women for expectant management or placebo	122 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a,b,c]
Misoprostol	1 trial used a visual analogue scale and found misoprostol had a score of 8.9 (+/- 1.3) compared to 8.7 (+/- 1.5) for expectant management or placebo with 52 women in each arm. 1 trial described 14 out of 16 (87.5%) women as being satisfied with misoprostol compared to 12 out of 16 (75%) women as being satisfied with expectant management or placebo	136 (2 RCTs)	⊕⊕⊖⊖ LOW[a,c]

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]-1 no meta-analysis possible, narrative synthesis was conducted, estimates are not precise
[b] -1 due to design limitations
[c] -1 due to imprecision

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BACKGROUND

Description of the condition

Miscarriage is the most common cause of pregnancy loss. An estimated 15% of pregnancies will end in miscarriage, with 25% of women experiencing a miscarriage in their lifetime (Alberman 1992). This can have emotional and physical impact on both women and their partners extending well beyond the pregnancy (Conway 2000; Geller 2001; Neugebauer 1997).

Miscarriage is generally defined as the spontaneous pregnancy loss before 24 weeks' gestation (Shiers 2003). Most miscarriages happen in the first 14 weeks, and are known as early miscarriages (Alberman 1992). The clinical signs of miscarriage are vaginal bleeding, usually with abdominal pain. Miscarriage can lead to serious morbidity, including haemorrhage and infection, and even death, particularly in low- and middle-income countries (MBRRACE-UK 2016, WHO 2018). A missed miscarriage, also known as a delayed or silent miscarriage, is diagnosed when a non-viable pregnancy is identified on ultrasound scan. Often, women who have missed miscarriage are asymptomatic or have small amounts of vaginal bleeding or pain before the diagnosis is made, but all pregnancy tissue is retained in the uterus. In contrast, incomplete miscarriage is diagnosed when pregnancy tissue has been partly expelled from the uterus (NICE 2019).

Description of the intervention

Miscarriage can be managed expectantly, medically, or surgically. Surgical methods have traditionally been used to manage early miscarriage. Dilatation and curettage uses sharp metal curettage that is often performed in an operating room under regional or general anaesthesia. Sharp curettage is often performed after dilatation of the cervix. Even though, it is a relatively simple procedure, it does carry a small chance of serious complications, such as anaesthetic complications, infection, uterine perforation and Asherman's syndrome. Suction aspiration (electrical or manual vacuum aspiration) has replaced sharp curettage in high-income countries and has a well-documented safety profile and is the recommended surgical method according to the World Health Organization (WHO) safe abortion guidelines (WHO 2009, WHO 2012a). Even so, it is less commonly used in low- and middle-income countries due to lack of equipment and experience. Surgical methods can be combined with an agent to prepare (or ripen) the cervix to avoid the risks of injury from cervical dilation. Commonly used agents include mechanical and pharmacological dilators. The mechanical dilators may use osmotic cervical rods, Foley catheters or laminaria to dilate the cervix. The pharmacological dilators cause cervical ripening by softening and dilation of the cervix. The most common pharmacological dilator is misoprostol, a synthetic prostaglandin E1 analogue that induces cervical ripening and uterine contraction. It is water-soluble and heat-stable (Davies 2001). Oral and sublingual routes have the advantage of rapid onset of action, while the vaginal and rectal routes result in prolonged activity and greater bioavailability (Schaff 2005). Misoprostol is, however, associated with side effects such as diarrhoea, abdominal pain, nausea and vomiting, shivering and pyrexia (Tunçalp 2012).

Medical methods of management of miscarriage include various agents. They usually involve a synthetic prostaglandin and the most commonly used prostaglandin is misoprostol. Other synthetic prostaglandins are available, such as gemeprost or dinoprost, but these agents are less frequently used in this setting. Mifepristone is a progesterone antagonist that interferes with the production or functioning of progesterone and can initiate shedding of pregnancy tissue. Mifepristone has been used alone for terminating unwanted pregnancies, but more frequently is used in combination with misoprostol to manage early miscarriage. It is considered to be more useful in women with missed miscarriages where a non-viable pregnancy is identified on ultrasound scan, and pregnancy tissue is retained in the uterus. In women with incomplete miscarriage, the anti-progesterone effect of mifepristone is considered less useful and treatment is aimed to stimulate uterine contractility often with misoprostol alone. Expectant management involves no surgical or medical intervention, with the expectation that the miscarriage will happen naturally.

Why it is important to do this review

Several Cochrane Reviews have compared an individual method for managing miscarriage with another method or with expectant management (Lemmers 2019; Kim 2017; Nanda 2012; Tuncalp 2010). However, a standard pairwise meta-analysis can only compare two methods that have been directly compared in head-to-head trials (direct evidence). In the absence of a single high-quality randomised controlled trial that compares all methods for managing miscarriage, uncertainty remains about which is the most effective. For the management of miscarriage with multiple competing treatment methods, not all of which have been directly compared, a network meta-analysis may be better able to allow for all possible comparisons to be made so we can determine which method is most effective (Caldwell 2005; Caldwell 2010). A network meta-analysis simultaneously pools all the available direct and indirect evidence on relative treatment effects, within a single coherent analysis. Indirect evidence is obtained by inferring the relative effectiveness of two competing methods through a common comparator. Thus, a network meta-analysis produces estimates of the relative effects of each method compared with every other in a network, even though some pairs may not have been directly compared, and has the potential to reduce the uncertainty in treatment effect estimates (Caldwell 2005). It also allows for the calculation of the probability that each method is the best for any given outcome and can be used to identify gaps in the evidence base (Caldwell 2005).

OBJECTIVES

To estimate the relative effectiveness and safety profiles for the different management methods for early miscarriage, and to provide rankings of the available methods according to their effectiveness, safety, and side-effect profile using a network meta-analysis.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled comparisons that assessed the effectiveness or safety of methods for miscarriage management. Cluster-randomised trials and quasi-randomised trials were eligible for inclusion. Randomised trials published only as abstracts were eligible if sufficient information could be retrieved. We excluded non-randomised trials.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Types of participants

We included all studies that included women who were being treated for early miscarriage (pregnancy loss at less than or equal to 14 weeks of gestation), diagnosed by ultrasound or clinically alone. We included women with both missed and incomplete miscarriage. Late miscarriages after 14 weeks of gestation (often referred to as intrauterine fetal deaths) was not eligible for inclusion in the review. We considered for inclusion studies conducted in all settings regardless of the age of women.

Types of interventions

All interventions were eligible for inclusion, and the following were included in the review: suction aspiration, suction aspiration plus cervical preparation, dilatation and curettage, mifepristone plus misoprostol, misoprostol, and expectant management or placebo.

We included regimens irrespective of their dose as long as they were in the therapeutic range that are recommended in international guidelines. Multi-arm trials that compared different dosages, regimens or routes of one drug, but also compared those versus another drug or method, were included. For the multi-arm trials, we merged the intervention arms of different dosages, regimens or routes of the same drug together for the global analysis of all outcomes and did not treat them as separate independent comparisons. We did not include trials that compared exclusively different dosages, regimens or routes of administration of the same drug. The review was restricted to studies that evaluated drugs or interventions administered by healthcare professionals.

We classified the comparisons within a study as follows:

- suction aspiration plus cervical preparation = any surgical management that involves suction aspiration with cervical preparation agents;
- suction aspiration = any surgical management that involves suction aspiration without any cervical preparation agents;
- dilatation and curettage = any surgical treatment involving sharp metal curette;
- mifepristone plus misoprostol = any medical management with the combined use of mifepristone plus misoprostol at any dose, route or regimen;
- misoprostol = any medical management with the use of misoprostol alone at any dose, route or regimen;
- expectant management = any management that does not involve any surgical or medical treatment.

Types of outcome measures

We estimated the relative effects and rankings of the competing methods of miscarriage management for the following outcomes.

Primary outcomes

- Complete miscarriage: this is defined as evidence of complete evacuation of uterine contents based on clinical findings or ultrasound examination after a specific time period as defined in the primary studies. Outcomes were pooled regardless of the timeframe for assessment.
- Composite outcome of death or serious complications (e.g. uterine perforation, need for further life-saving procedures including hysterectomy, blood transfusion or intensive care unit admission).

Secondary outcomes

- Need for unplanned/emergency surgical procedure.
- Pain scores (visual analogue scale).
- Pelvic inflammatory disease, sepsis or endometritis.
- Mean volumes of blood loss (mL).
- Change in haemoglobin measurements before and after the miscarriage.
- Days of bleeding.
- Cervical tear.
- Women's views or satisfaction.
- Mean duration of hospital stay (days).
- Re-admission to hospital.
- Nausea.
- Vomiting.
- Diarrhoea.
- Pyrexia.
- Anxiety score.
- Depression score.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (9 February 2021).

The Register is a database containing over 27,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. hand searches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

has been fully accounted for in the relevant review sections (Included studies, Excluded studies, Studies awaiting classification or Ongoing studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (Feb 12 2021) using the terms listed in Appendix 1.

Searching other resources

We retrieved additional relevant references cited in papers identified through the above search strategy. We screened citations and abstracts and searched for the full texts of studies identified as abstracts. If required, we sought information from primary authors to investigate whether these studies meet eligibility criteria, and to obtain outcome and study data. If this was not possible, we only included abstracts if we could extract sufficient information to satisfy our eligibility criteria and the study authors reported the outcomes of interest. Trials that compared at least two of the drugs or interventions were eligible and we searched for all possible comparisons formed by the drugs or interventions of interest. We did not apply any language or date restrictions.

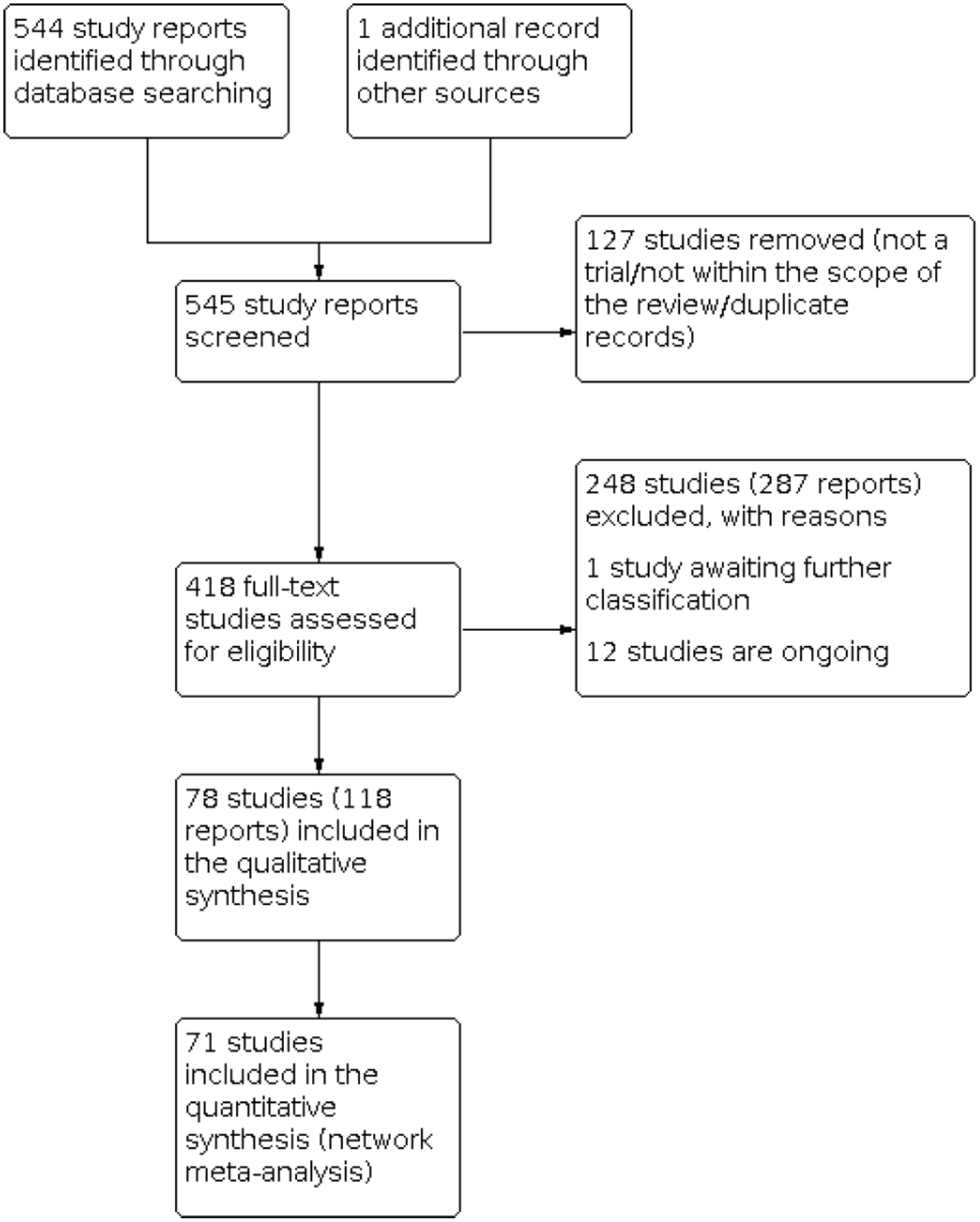
Data collection and analysis

Selection of studies

At least two review authors (JG, HJ, VD) retrieved and independently assessed for inclusion all the potential studies we identified as a result of the search strategy. Any disagreements were resolved through discussion or, when required, with consultation with a third review author (IDG). We created a PRISMA study flow diagram to map out the number of records identified, included and excluded (Figure 1).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 1. Study flow diagram.



Data extraction and management

We designed an electronic form to extract data. For eligible studies, at least three review authors (JG, AP, HJ, AD, LB, VD) independently extracted the data using the form. We resolved discrepancies through discussion or, when required, with consultation with a seventh review author (IDG). We entered data into Review Manager

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

5 (RevMan 5.4) software and it was checked for accuracy (RevMan 2014). When information regarding any of the above was unclear, we attempted to contact the authors of the original reports to provide further details. We extracted the following data.

Methods extracted

1. Study design
2. Sequence generation
3. Allocation sequence concealment
4. Blinding
5. Attrition
6. Study protocol and inconsistencies compared with the published report
7. Financial support and conflicts of interest
8. Other concerns about bias

Data extracted

From each included study we extracted the number of participants, along with the inclusion and exclusion criteria. We also extracted the interventions being compared including the healthcare setting, and their respective primary and secondary outcomes relevant to this review. We extracted all relevant arm level data (e.g. number of events and number of participants for binary outcomes and means and standard deviations per study arm for continuous outcomes). Participants in the network could in principle have been randomised to any of the methods being compared. For example, a woman with an early miscarriage could be equally likely to be randomised to dilatation and curettage, misoprostol, suction aspiration, suction aspiration plus cervical preparation, mifepristone plus misoprostol or expectant management or placebo. All of these six interventions were of direct interest.

Data on potential effect modifiers

From each included study we extracted the following study, intervention and population characteristics that may act as effect modifiers:

- gestational age (less than or equal to nine weeks versus greater than nine weeks of gestation);
- type of miscarriage (incomplete versus missed miscarriage);
- healthcare setting (inpatient versus outpatient);
- dosage, regimen, and route of drug administration (sublingual, rectal, oral).

Other data

From each included study we extracted the following additional information:

- country or countries in which the study was performed;
- date of publication;
- type of publication (full-text publication, abstract publication, unpublished data);
- trial registration reference.

Assessment of risk of bias in included studies

At least two review authors (JG, HJ, AD, LB, VD) independently assessed the risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving another review author (AP, IDG).

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

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the methods as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

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

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

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as at:

- low, high or unclear risk of bias.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state 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 has been supplied by the trial authors, we have re-included missing data in the analyses which we undertook.

We assessed methods as at:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups or not exceeding 10% for the primary outcomes of the review);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation or exceeding 10% for the primary outcomes of the review);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias.

We assessed the methods as:

- low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so cannot be used; the study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

We described for each included study any important concerns we have about other possible sources of bias.

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

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses (see the 'Sensitivity analysis' section). For our primary outcomes, we combined quality items and judged trials as "A" if they were at low risk of bias and if they include an adequate random sequence generation, allocation concealment, blinding, no selective reporting and with little loss to follow-up (less than 10%) and free of other bias. Trials were judged at "B" if they were at moderate risk of bias and if they demonstrated serious limitations in key criteria excluding randomisation and allocation concealment, for example unclear concealment of allocation. Alternatively, trials were considered to be "C" or at high risk of bias if they had serious limitations in the randomisation sequence (quasi-randomised) or lack of allocation concealment, or small blocked randomisation (<10) or other very serious, crucial methodological limitations such as lack of blinding for a subjective outcome. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis for information about how the risk of bias was incorporated in the sensitivity analysis.

Measures of treatment effect

Relative treatment effects

For dichotomous data, we present results as a summary risk ratio (RR) with 95% confidence interval (CIs). For continuous data, we used the mean difference (MD) if outcomes are measured in the same way between trials. We used the standardised mean difference (SMD) to combine trials that measured the same outcome, but used different methods. If the target parameter is the effect of change in a continuous measure, such as the change in haemoglobin between baseline and post-miscarriage, where possible, we accounted for the within-patient correlation between baseline and post-miscarriage estimates (Dias 2013). For the network meta-analysis (NMA,) zero events were handled by deleting the relevant cells. These are summarised in forest plots displaying the results from pairwise, indirect and network (combining direct and indirect) analyses for the comparisons between the different methods of miscarriage management.

Relative treatment ranking

We also estimated the ranking probabilities for all methods of miscarriage management of being at each possible rank for each intervention (conditional on the model and specified vague priors). Then we obtained 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; the larger the SUCRA the higher its rank among all available methods (Salanti 2011). The probabilities to rank the treatments are estimated under a Bayesian model with flat priors, assuming that the posterior distribution of the parameter estimates is approximated by a normal distribution with mean and variance equal to the frequentist estimates and variance–covariance matrix. Rankings are constructed drawing 1000 samples from their approximate posterior density. For each draw, the linear predictor is evaluated for each study, and the largest linear predictor is noted (White 2011).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually-randomised trials. We planned to adjust their sample sizes using the methods described in the Handbook (Higgins 2011), using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population. If we had used ICCs from other sources, we planned to report this and to conduct sensitivity analyses to investigate the effect of variation in the ICC. Had we identified both cluster-randomised trials and individually-randomised trials, we planned to synthesise the relevant information. In cluster-randomised trials, particular biases to consider include:

- recruitment bias;
- baseline imbalance;
- loss of clusters;
- incorrect analysis; and
- comparability with individually-randomised trials.

We would have considered it reasonable to combine the results from both cluster-randomised trials and individually-randomised trials if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely. We planned to also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit. We planned to include cluster-randomised trials in the analyses along with individually-randomised trials, but none were found.

Cross-over trials

Cross-over trials are not eligible for inclusion in this review.

Multi-arm trials

We included multi-arm trials and accounted for the correlation between the effect sizes in the network meta-analysis. We treated multi-arm studies as multiple independent comparisons in pairwise meta-analyses.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. We imputed missing standard deviations and errors using standard techniques where possible (Higgins 2011). For all outcomes, we performed analyses, as far as possible, on a modified intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and we analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity

To evaluate the presence of clinical heterogeneity, we examined trial and study population characteristics across all eligible trials that compared each pair of interventions. We assessed the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics.

Assessment of transitivity across treatment comparisons

We assessed the assumption of transitivity by comparing the distribution of potential effect modifiers across the different pairwise comparisons. In this context we expect that the transitivity assumption will hold assuming the following: 1) the common treatment used to compare different miscarriage management drugs indirectly is similar when it appears in different trials (e.g. misoprostol is administered in a similar way in misoprostol versus suction aspiration trials and in misoprostol versus mifepristone plus misoprostol trials); 2) all pairwise comparisons do not differ with respect to the distribution of effect modifiers (e.g. the design and study characteristics of suction aspiration versus misoprostol trials are similar to misoprostol versus mifepristone plus misoprostol trials).

Assessment of statistical heterogeneity and inconsistency

Assumptions when estimating the heterogeneity

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

Measures and tests for heterogeneity

We assessed statistically the presence of heterogeneity within each pairwise comparison using the I^2 statistic and its 95% CI that measures the percentage of variability that cannot be attributed to random error (Higgins 2002). We based the assessment of statistical heterogeneity in the entire network on the magnitude of the heterogeneity variance parameter ($\tau 2$) estimated from the network meta-analysis models. For dichotomous outcomes we compared the magnitude of the heterogeneity variance with the empirical distribution as derived by Turner (Turner 2012). We also estimated a total I^2 statistic value for heterogeneity in the network as described elsewhere (Higgins 2002). The certainty of the evidence was downgraded for inconsistency where $I^2 \geq 60\%$ in line with the World Health Organization standard operating procedures for grading evidence for guidelines (Vogel 2019).

Assessment of statistical inconsistency

The statistical agreement between the various sources of evidence in a network of interventions (consistency) was evaluated by global and local approaches to complement the evaluation of transitivity.

Local approaches for evaluating inconsistency

To evaluate the presence of inconsistency locally we used the loop-specific approach. This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor) (Veroniki 2013). Then, the magnitude of the inconsistency factors and their 95% CIs can be used to infer about the presence of inconsistency in each loop. We assumed a common heterogeneity estimate within each loop.

Global approaches for evaluating inconsistency

To check the assumption of consistency in the entire network we used the "design-by-treatment" model as described by Higgins

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

and colleagues (Higgins 2012). This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach we inferred about the presence of inconsistency from any source in the entire network based on a Chi^2 test. We performed the design-by-treatment model in STATA using the mvmeta command (StataCorp. 2019).

Inconsistency and heterogeneity are interwoven; to distinguish between these two sources of variability we employed the I^2 statistic for inconsistency that measures the percentage of variability that cannot be attributed to random error or heterogeneity (within comparison variability).

Assessment of reporting biases

We aimed to minimise the potential impact of these biases by ensuring a comprehensive search for eligible studies and by being alert to duplication of data. If there were 10 or more studies in any of the direct comparisons, we investigated reporting biases (such as publication bias) using funnel plots to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies) as part of the assessment of the certainty of the direct evidence.

Data synthesis

Methods for direct treatment comparisons

We performed standard pairwise meta-analyses using a random-effects model in Review manager software (Revman 5.4) for every treatment comparison (DerSimonian 1986). The random-effects method (DerSimonian 1986) was used for this analysis to mitigate for the high level of heterogeneity observed. This method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. The standard errors of the study-specific estimates are therefore adjusted to incorporate a measure of the extent of heterogeneity. This results to wider confidence intervals in the presence of heterogeneity, and corresponding claims of statistical significance are more conservative.

Methods for indirect and mixed comparisons

We initially generated and assessed the network diagrams to determine if a network meta-analysis was feasible. Then we performed the network meta-analysis within a frequentist framework using multivariate meta-analysis estimated by restricted maximum likelihood. All analyses were done using Stata statistical software, release 15 (StataCorp, College Station, TX). We used the network suite of Stata commands designed for this purpose (White 2012; White 2015).

Subgroup analysis and investigation of heterogeneity

For the primary outcomes we had planned to carry out the following pre-specified subgroup analyses by using the following effect modifiers.

- gestational age (greater than nine weeks versus less than or equal to nine weeks of gestation);
- type of miscarriage (incomplete versus missed miscarriage);
- type of vacuum aspiration device used (electrical versus manual vacuum aspiration);
- type of healthcare setting (inpatient versus outpatient);
- dosage, regimen, and route of drug administration (sublingual, rectal, oral).

We assessed subgroup differences by evaluating the relative effects and assessment of model fit for the primary outcome of complete miscarriage.

Sensitivity analysis

For the primary outcomes we had planned to perform sensitivity analysis for the following:

- overall risk of bias of the studies (restricted to studies at low risk of overall bias);
- randomisation unit (cluster versus individual);
- use of placebo versus expectant management.
- exclusion of quasi-randomised trials

We assessed differences by evaluating the relative effects and assessment of model fit.

Summary of findings and assessment of the certainty of the evidence

The summary of findings tables present evidence comparing all methods with a reference comparator, expectant management or placebo. Each table describes key features of the evidence relating to a single outcome. There is a table for each important outcome in accordance with the GRADE approach. These outcomes are 1) complete miscarriage, 2) composite outcome of death or serious complication, 3) need for unplanned/emergency surgical procedure, 4) pain scores (visual analogue scale), 5) pelvic inflammatory disease, sepsis or endometritis, 6) days of bleeding, and 7) women's views or satisfaction. We also present tables for two subgroups analyses of the complete miscarriage outcome: 1) missed miscarriage and 2) incomplete miscarriage. We assessed the certainty of the evidence using the GRADE approach as outlined in the GRADE handbook in order to assess the certainty of the body of evidence relating for each outcome for all comparisons. In order to create summary of findings tables, we used GRADEpro GDT, to import data from RevMan 5.4 (RevMan 2014).

We used the GRADE working group's approach (Brignardello-Petersen 2018; Puhan 2014) for rating the certainty of the network meta-analysis effect estimates for all the comparisons and all outcomes. We appraised the certainty of the direct, indirect, and network evidence sequentially (in this order). First, we assessed the certainty of the direct evidence (where available) for a given outcome, and rated the evidence using the standard GRADE approach based on consideration of: study design limitations (risk of bias); inconsistency; imprecision; indirectness and publication bias (Higgins 2011). Study design limitations were assessed using an A, B or C scale with "A" studies being at low risk of bias and "C" studies being at high risk of bias as described before. For objective outcomes, importance was given to method of randomisation, allocation concealment and attrition bias, whereas for subjective outcomes blinding of the assessor was also taken into consideration. On all the network diagrams, of the outcomes where network meta-analysis was possible, we display the certainty of the direct evidence using a colour-coded key as outlined in the figure caption. Then we rated the certainty of the indirect evidence for the same given outcomes, and this was determined based on the lower

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

of the certainty ratings of the two direct arms forming the dominant 'first-order' loop in the network diagram for this outcome. Our final step was to determine the certainty of network evidence based on: (i) the higher certainty rating of the direct and indirect evidence, (ii) whether the relevant network exhibited 'transitivity', i.e. whether all the comparisons contributing data to the estimate were directly consistent with the PICO question, (iii) consideration of coherence between direct and indirect effect estimates, and (iv) precision of the network effect estimate. At each of these stages, two review authors (JG, AP) independently appraised the certainty ratings for the direct, indirect and network evidence. Disagreements between authors were resolved through discussion and consultation with a third review author (IDG) where necessary.

The certainty of network evidence for each outcome was rated as 'high', 'moderate', 'low' or 'very low' in accordance with the GRADE approach.

- 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.

For ease of comparison when interpreting the relative effects of all methods for managing a miscarriage compared to expectant management or placebo, the summary of findings tables include the effect estimate and certainty judgements for each of the direct evidence, indirect evidence and the network meta-analysis, describing all the findings for a single outcome in each table. The anticipated absolute effects are also included, based on the network effect estimate for each treatment intervention in comparison with expectant management or placebo. The assumed risks in the expectant management or placebo group are based on weighted means of baseline risks from the studies with expectant management or placebo arms in the network meta-analysis. The corresponding risks in the suction aspiration plus cervical preparation, suction aspiration, dilatation plus curettage, mifepristone plus misoprostol, misoprostol groups (and their 95% CIs) are based on the assumed risk in the expectant management or placebo group and the relative effect of the individual treatment intervention, when compared with the expectant management or placebo group (and its 95% CI) as derived from the network meta-analysis.

RESULTS

Description of studies

Results of the search

The results of the search are summarised in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1). The search of Cochrane Pregnancy and Childbirth's (CPC) Trials Register on 9 February 2021 retrieved in total 544 available records. One further record from additional author searches and manual searching of reference lists was obtained. We excluded 127 records as duplicates or based on their title and abstract. We examined the full text of 418 records and included in the network meta-analysis 78 randomised trials (reported in 118 publications). We contacted the authors from 38 references for additional data or clarifications. We were able to obtain additional data or clarifications from trial authors for nine randomised trials (Characteristics of included studies). We excluded 248 studies (reported in 287 publications) (Characteristics of excluded studies), one trial (reported in one publication) could not be classified (Characteristics of studies awaiting classification) and 12 studies were still ongoing (Characteristics of ongoing studies).

Included studies

This review included 78 randomised trials, published between 1979 and 2021, involving 17,795 women. All studies were individually randomised; there were no cluster-randomised studies. A number of multi-arm trials were identified: three four-arm trials and five three-arm trials. For the three four-arm trials as there was randomisation based on setting of care as well as intervention, the arms which had the same intervention were combined for the purposes of the network meta-analysis. For two of the three-arm trials, one arm was excluded from the analysis due to reasons detailed in the table of Characteristics of included studies. Most studies were reported in English (86%, 67/78); Four translations were obtained (three Portuguese and one Norwegian). One study was funded by Assistance Publique Hôpitaux de Paris, France (Torre 2012); one study was funded by Committee on Research and Conference Grants, University of Hong Kong (Ngai 2001); two studies were funded by the David and Lucille Packard Foundation (Dabash 2010, Taylor 2011); one study was funded by the Health Services Research Fund of Hong Kong (Chung 1999); one study was funded by the Healthcare Insurers Innovation Foundation, Canada (Hamel 2021); one study was funded by National Institute for Health Research HTA programme, UK (Chu 2020); four studies were funded by National Institutes of Health, USA (Zhang 2005; Davis 2007; Harwood 2008; Schreiber 2018); one study was funded by the Riverside Methodist Hospital Medical Research Foundation, USA (Lister 2005); one study was funded by a South and West NHS Executive research and development grant, UK (Trinder 2006); one study was funded by the Swedish Medical Research Council (Nielsen 1995). All the other 64 studies did not state their source of funding. One study declared consultancy fees from Danco laboratories as a conflict of interest (Schreiber 2018); one study declared the donation of £20,000 from Exelgyn, the manufacturers of mifepristone, which was an intervention used in the trial as a conflict of interest (Trinder 2006); one study declared that two authors had served as consultants to Pfizer as a conflict of interest (Zhang 2005). Ten studies stated that there were no conflicts of interest to declare from any of the authors, and 65 studies did not state whether the authors had any conflicts of interest.

The studies were conducted across 37 countries (including high-, middle- and low-income countries); there were no multi-country trials. The median size of the trials was 180 participants (interquartile range (IQR) 206 (94 to 300)). Most studies were single-centre studies (82%, 64/78); 14 studies were multi-centre studies (18%, 14/78). Most trials (91%, 71/78) were performed in a hospital setting, four were performed in a community setting (5%), two (3%) in a mixed setting, and one (1%) of unspecified setting. Six of the studies only recruited women with an early first trimester miscarriage (less than or equal to nine weeks of gestation) with

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

the majority (61/78) only specifying a gestational age of less than or equal to 14 weeks of gestation; a specific cut-off in terms of gestational age was not specified in 11 out of 78 studies. Thirty-six out of 78 studies were based purely on women with an incomplete miscarriage, 17 studies on women with a missed miscarriage, 19 had a mixed population of women with either a missed or incomplete miscarriage and in six studies the type of miscarriage was not specified.

Of the 78 included studies, 71 (90%) contributed data to the analysis, seven studies did not present the data in a usable form for meta-analysis or narrative synthesis. Across the 71 trials (158 trial arms) that contributed data for analysis, the following agents were used either as intervention or comparison:

- 51 trial arms (33%) used misoprostol;
- 50 trial arms (32%) used suction aspiration;
- 26 trial arms (16%) used expectant management or placebo;
- 17 trial arms (11%) used dilatation and curettage;
- 11 trial arms (6%) used mifepristone plus misoprostol;
- 3 trial arms (2%) used suction aspiration plus cervical preparation.

Of the 51 trial arms that used misoprostol, the concentrations of the first dose administered were as follows: 19 of 51 (37%) used 800 micrograms, 17 of 51 (33%) used 400 micrograms, 13 of 51 (23%) used 600 micrograms, 1 of 51 (2%) used 200 micrograms, and 1 of 51 (2%) did not specify the dose of misoprostol. The routes of administration used for misoprostol was as follows: 26 of 51 (51%) gave misoprostol vaginally, 19 of 51 (37%) orally, 2 of 51 (4%) vaginally or orally, 2 of 51 (4%) sublingually, and 2 of 51 (4%) did not specify the route of administration.

Of the 11 trial arms that assessed the effectiveness of mifepristone, six of 11 (55%) used a 200 milligram dose of mifepristone, four of 11 (36%) used a 600 milligram dose and one of 11 (9%) used a dose of 400 milligrams. Mifepristone was always taken orally and given in combination with misoprostol, which was taken 24 to 72 hours later. The concentrations of misoprostol administered following mifepristone were as follows: 7 of 11 (64%) used 800 micrograms and 4 of 11 (36%) used 400 micrograms of misoprostol. The routes of administration for misoprostol following mifepristone were as follows: 5 of 11 (46%) gave misoprostol vaginally, 3 of 11 (27%) orally, and 3 of 11 (27%) vaginally or orally.

Of the 59 trials that contributed to the primary outcome, 14 (24%) made the assessment for complete miscarriage on days 1 to 5, 14 (24%) on day 7, 18 (31%) on days 10 to 14 and 9 (15%) over 15 days later. 4 studies (6%) did not specify the timeframe used to assess complete miscarriage.

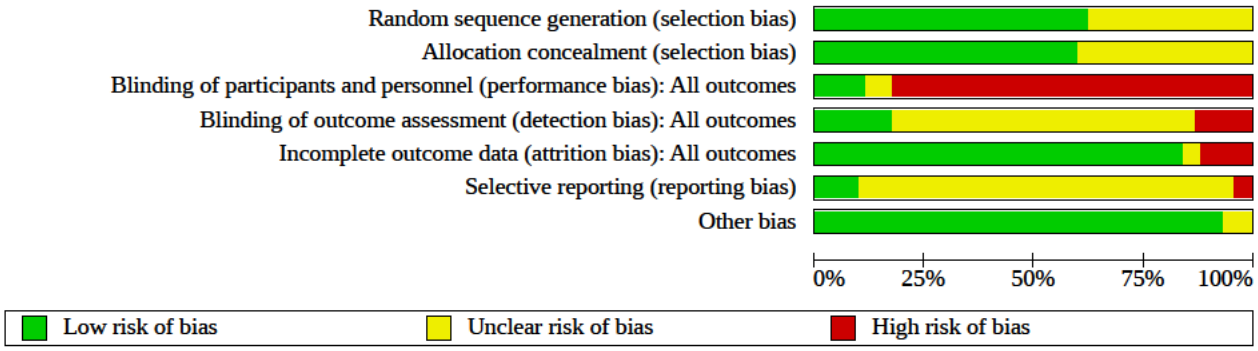
Excluded studies

We excluded 248 trials (for details see Characteristics of excluded studies). The most common reasons for exclusion were because trials included participants who were over 14 weeks of gestation at the time of recruitment or were based on participants undergoing a termination of pregnancy. Some trials were not randomised, or exclusively investigated doses or routes of administration of the same method of management of miscarriage.

Risk of bias in included studies

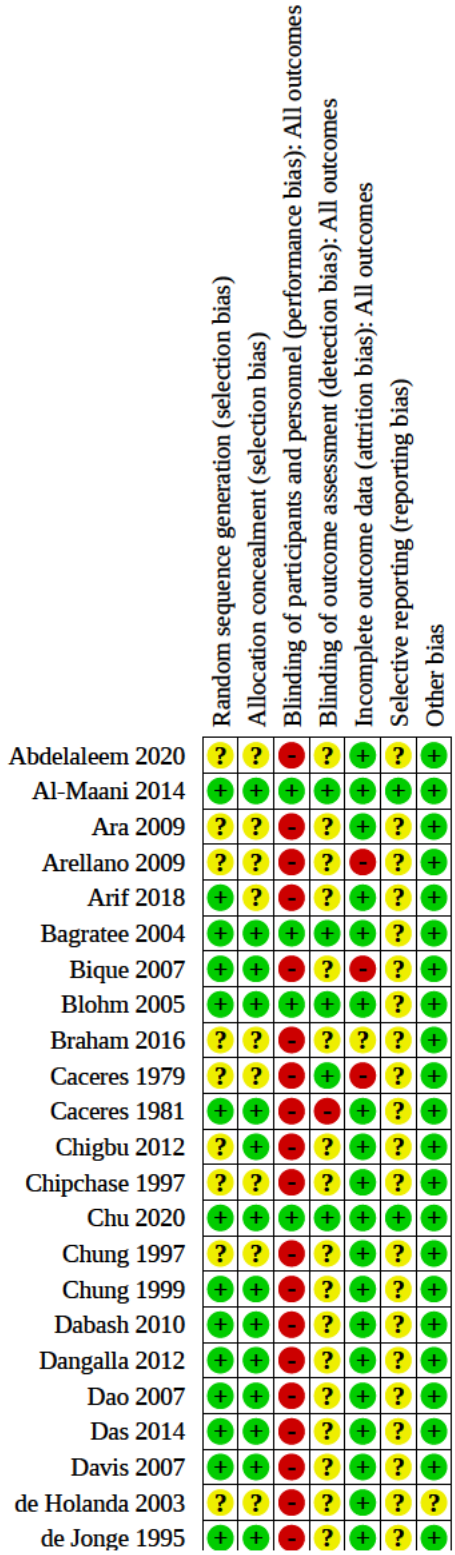
We present summaries of the risk of bias of the included studies for each of the domains we assessed across all studies (Figure 2) and for each included study (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



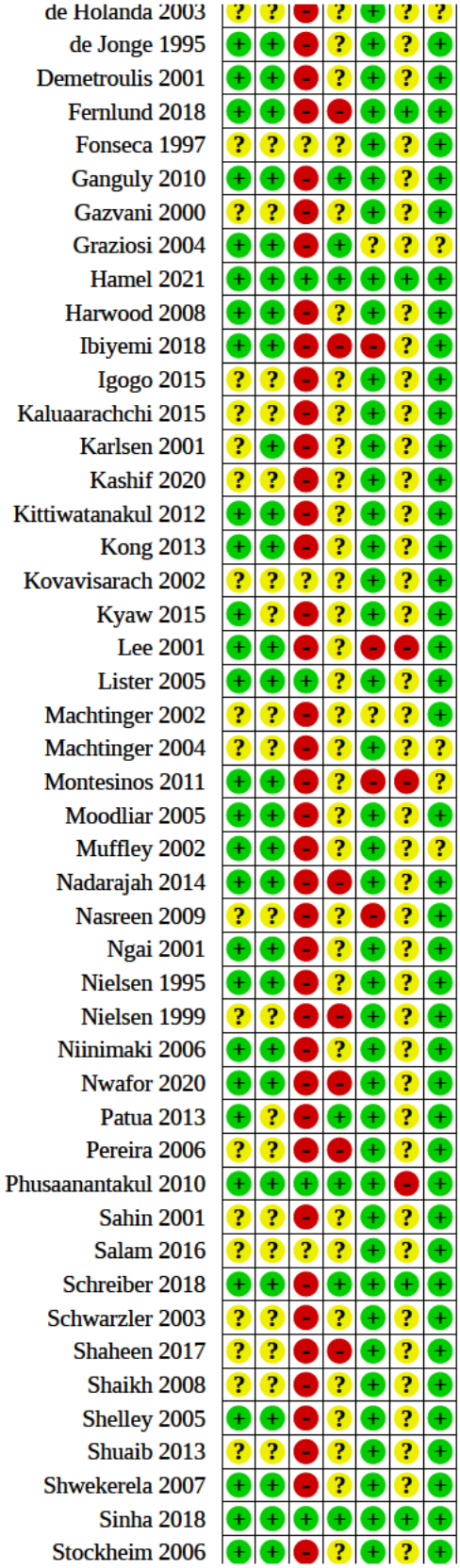
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



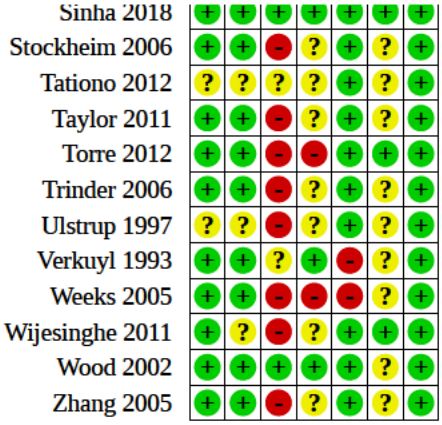
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 3. (Continued)



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 3. (Continued)



Allocation

Adequate sequence generation was found to have been used in 49 of 78 trials (63%) and these trials were judged to be at low risk of bias. In 29 of 78 trials (37%) the description of sequence generation was not clearly stated and hence they were at unclear risk of bias. In 47 of 78 trials (60%) there was a clear description of adequate allocation concealment. However, in 31 of 78 trials (40%) the description of allocation concealment was inadequate and so these trials were at unclear risk of bias. Many of the trials with inadequate information about sequence generation or allocation concealment were abstracts or other forms of short communications, which had limited word counts. Most of the trials which had inadequate description of random sequence generation also gave inadequate information regarding allocation concealment.

Blinding

Only 9 of 78 trials (12%) had blinding of participants and personnel and hence were judged to be at low risk of bias. Four of 78 trials (5%) had unclear information regarding blinding of patients and personnel and were therefore judged to be at unclear risk of bias with the remaining 65 of 78 trials (83%) unblinded to either patients or personnel or both and therefore at high risk of bias. In the majority of these unblinded trials, the nature of the intervention and comparator, for example with misoprostol versus suction curettage, meant blinding was not practically possible rather than being a result of poor trial design. Blinding of the outcome assessor of the primary outcome of complete miscarriage was inadequately described in 56 of 78 trials (72%) meaning these were judged to be at unclear risk of bias. In 9 of 78 trials (12%) the outcome assessor was unblinded meaning these were at high risk of bias. Only in 12 of 78 trials (15%) was it clearly stated that the outcome assessor was blinded meaning these trials were at low risk of bias.

Incomplete outcome data

There were 66 of 78 trials (85%) that had minimal missing outcome data (less than 10%) and balanced in numbers across intervention groups with similar reasons for missing data across groups, and were therefore at low risk of attrition bias. Nine of 78 trials (12%) were judged to be at high risk of attrition bias due to losing over 10% of their participant population to follow up. Three of 78 trials (3%) were judged to be at unclear risk of attrition bias as not enough information was provided to assess whether or not the handling of incomplete data was appropriate.

Selective reporting

Only eight of 78 trials (10%) pre-specified all outcomes in publicly available study protocols and were judged to be at low risk of reporting bias. Three of 78 trials (4%) did not report all pre-specified outcomes as reported in their published protocols or methodology within the main report and were judged to be at high risk of bias for selective reporting. For most trials (67 of 78 trials; 86%), we were unable to identify a published protocol and the risk of reporting bias was judged to be unclear.

Other potential sources of bias

In 73 of 78 trials (94%) there were no other potential sources of bias detected and so these were judged to be at low risk of bias. Five of 78 trials (6%) were judged to be at unclear risk of bias; one because it was not explained why one arm of the trial was greater than 50% larger than the other arm despite random allocation and no indication of randomisation other than in a 1:1 ratio, one because a vaginal lubricant was co-administered with the vaginal misoprostol for some participants which the authors acknowledge may have affected the rate of absorption of the medication, one because the method of outcome assessment varied between sites where the trial was conducted, and one because the research group accepted a donation of £20,000 from Exelgyn, the manufacturers of mifepristone. The majority of comparisons contained less than 10 studies, therefore investigation of publication bias was not valid. The comparison of suction aspiration vs misoprostol for the outcomes of nausea, vomiting and diarrhoea were downgraded for publication bias.

Overall risk of bias

For the comparison of suction aspiration versus misoprostol, 7 of 23 (30%) trials were judged to be at high overall risk of bias, and 16 of 23 (70%) trials at low overall risk of bias. For the comparison of suction aspiration versus dilatation & curettage, 2 of 5 (40%) trials were judged to be at high overall risk of bias, and 3 of 5 (60%) at low overall risk of bias. For the comparison of misoprostol versus mifepristone plus misoprostol, 2 of 7 (29%) trials were judged to be at high overall risk of bias, and 5 of 7 (71%) at low overall risk of bias. For the comparison of misoprostol versus dilatation & curettage,

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

2 of 4 (50%) trials were judged to be at high overall risk of bias, and 2 of 4 (50%) at low overall risk of bias. For the comparison of misoprostol versus suction aspiration plus cervical preparation, the single trial was judged to be at high overall risk of bias. For the comparison of misoprostol versus expectant or placebo, 1 of 10 (10%) trials were judged to be at high overall risk of bias, and 9 of 10 (90%) at low overall risk of bias. For the comparison of mifepristone plus misoprostol versus expectant or placebo, 1 of 3 (33%) trials were judged to be at high overall risk of bias, and 2 of 3 (67%) at low overall risk of bias. For the comparison of suction aspiration versus mifepristone plus misoprostol, suction aspiration versus expectant or placebo, and dilatation & curettage versus expectant or placebo, all trials were judged to be at low overall risk of bias.

Effects of interventions

See: **Summary of findings 1** Complete miscarriage; **Summary of findings 2** Complete miscarriage (missed miscarriage subgroup); **Summary of findings 3** Complete miscarriage (incomplete miscarriage subgroup); **Summary of findings 4** Composite outcome of death or serious complication; **Summary of findings 5** Need for unplanned/emergency surgical procedure; **Summary of findings 6** Pain scores (visual analogue scale); **Summary of findings 7** Pelvic inflammatory disease, sepsis or endometritis; **Summary of findings 8** Days of bleeding; **Summary of findings 9** Women's views/satisfaction

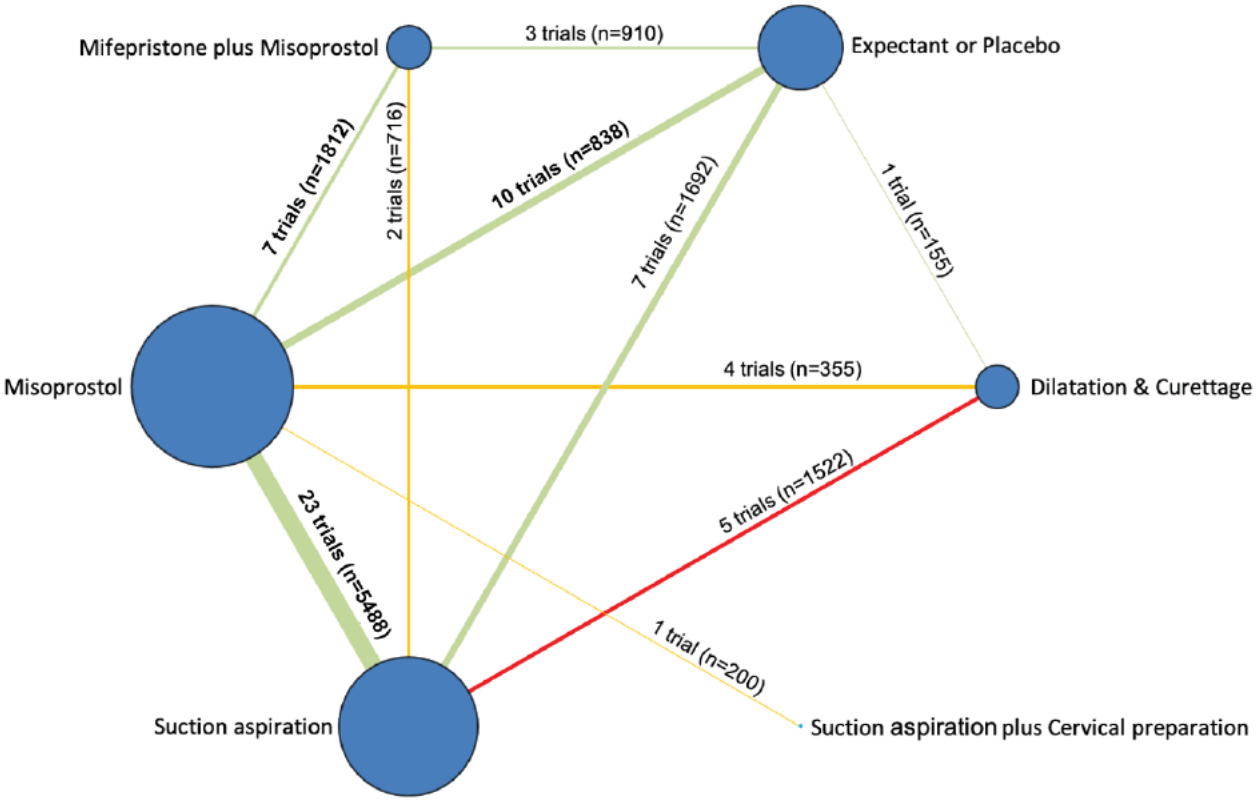
See: Summary of findings 1 for the main comparison "complete miscarriage" and Summary of findings 4 for the second primary outcome "composite outcome of death or serious complication". Summary of findings 5, Summary of findings 6, Summary of findings 7, Summary of findings 8 and Summary of findings 9, present the effects of interventions from other important secondary outcomes such as "need for unplanned/ emergency surgical procedure", "pain scores (visual analogue scale)", "pelvic inflammatory disease, sepsis or endometritis", "days of bleeding", "women's views or satisfaction" respectively. Summary of findings 2 and Summary of findings 3 present the effects of the subgroup analyses of women with a missed miscarriage and women with an incomplete miscarriage respectively for the primary outcome of "complete miscarriage".

Please note that all of the analyses presented in the Data and analyses section relate to the 'direct evidence' and were used as per our methods to grade the evidence. The results from Data and analyses were also used to check the direction of effect in the subgroups, and subgroup analyses are presented for the outcome of complete miscarriage where a high level of global statistical inconsistency and heterogeneity was observed.

The following section presents the results as reported in all of the figures (Figure 4 to Figure 5). The figures present the results from the network diagrams, the forest plots with the pairwise, indirect and network (combining direct and indirect) effect estimates and the cumulative rankograms for all the outcomes with available data. The figures present the results for different methods for managing miscarriage in comparison to expectant management or placebo and different methods for managing miscarriage.

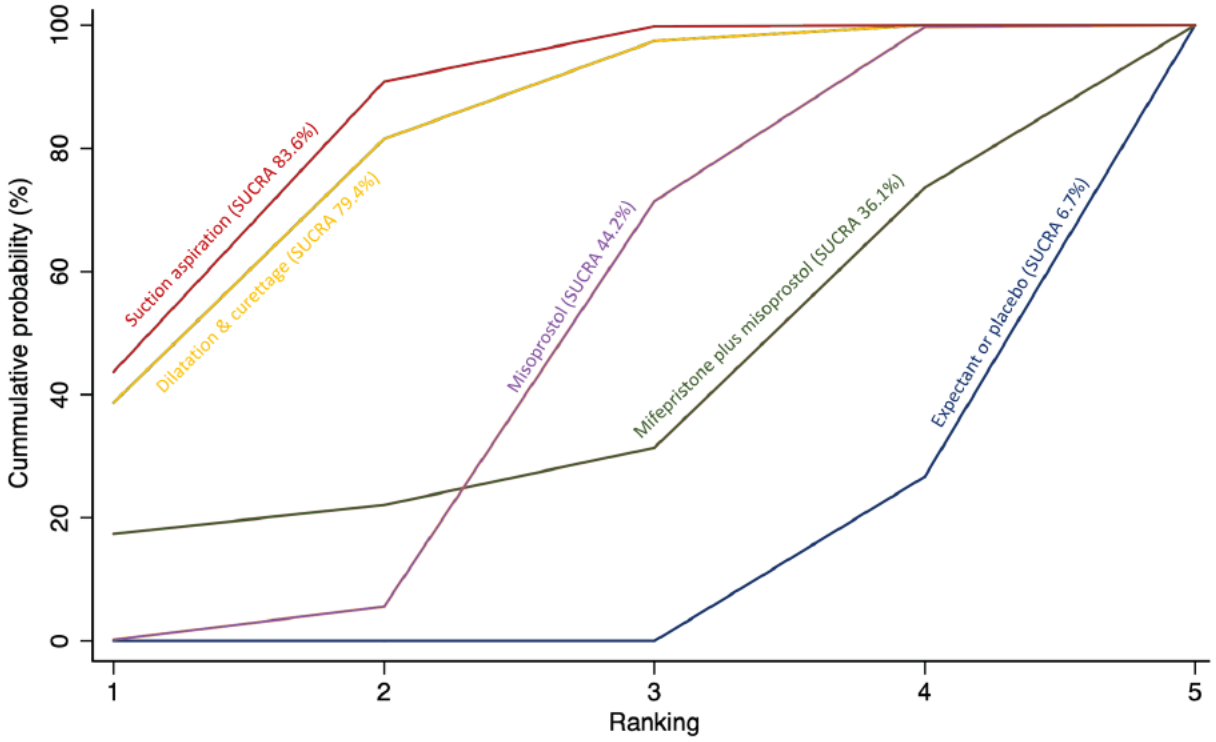
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 4. Network diagram for outcome of complete miscarriage. 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 and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 5. Cumulative rankogram comparing each of the methods of management of a miscarriage for incomplete miscarriage subgroup analysis for the outcome of complete miscarriage. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.



Primary outcomes

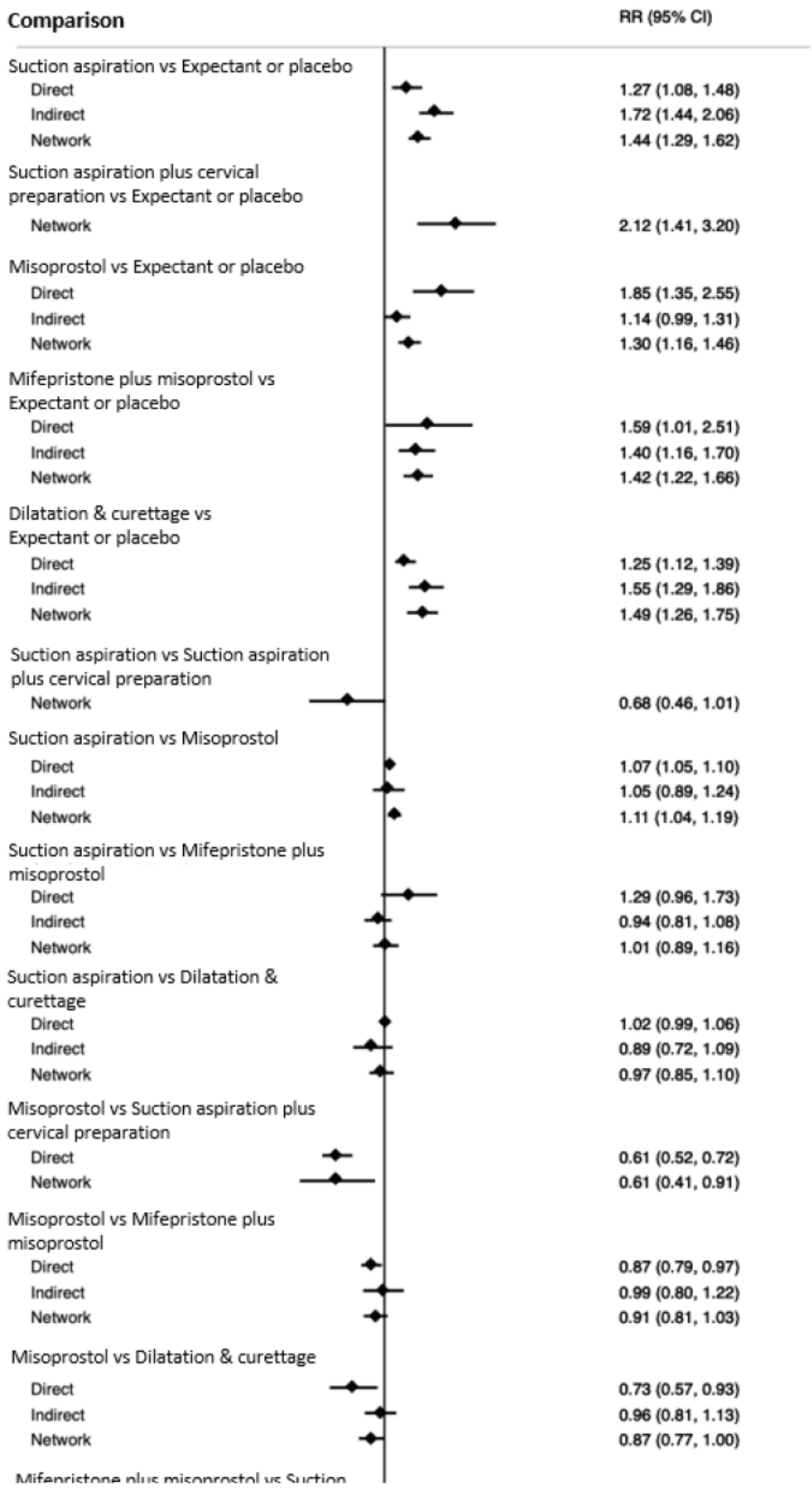
Complete miscarriage

The network diagram for the outcome of complete miscarriage is presented in Figure 4. Misoprostol was the most frequently investigated method of miscarriage management (45 of 63 trial arms [71%]) for this outcome (Figure 4).

Relative effects from the network meta-analysis of 59 trials, suggested that suction aspiration plus cervical preparation (risk ratio (RR) 2.12, 95% confidence interval (CI) 1.41 to 3.20, *low-certainty evidence*), dilatation and curettage (RR 1.49, 95% CI 1.26 to 1.75, *low-certainty evidence*), suction aspiration (RR 1.44, 95% CI 1.29 to 1.62, *low-certainty evidence*), mifepristone plus misoprostol (RR 1.42, 95% CI 1.22 to 1.66, *moderate-certainty evidence*) and misoprostol (RR 1.30, 95% (CI) 1.16 to 1.46, *low-certainty evidence*) may be more effective in achieving complete miscarriage compared with expectant management or placebo (Figure 6; Summary of findings 1).

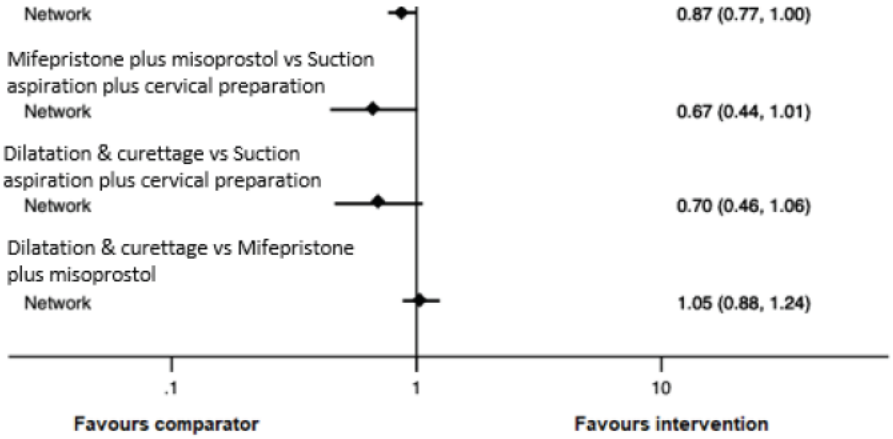
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 6. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for outcome of complete miscarriage.



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 6. (Continued)

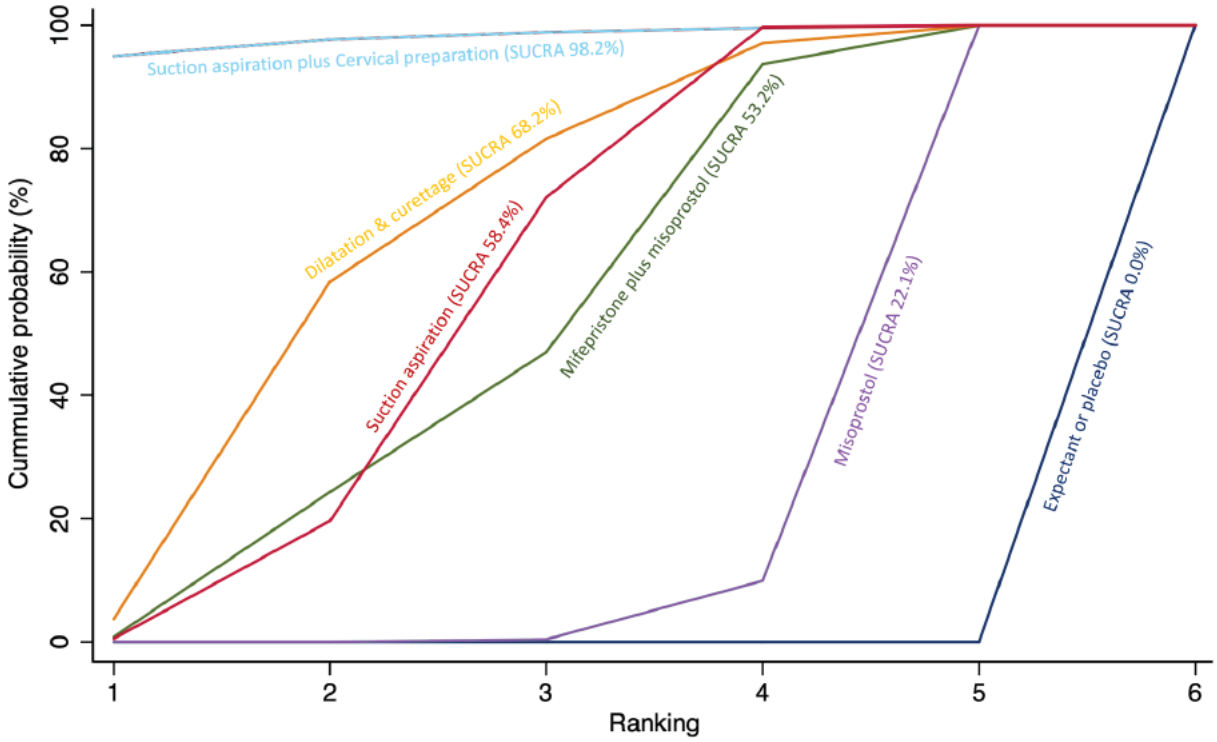


Based on these results, about 640 per 1000 women having expectant management or placebo would have a complete miscarriage compared with 1000 having suction aspiration plus cervical preparation, 954 for dilatation and curettage, 922 for suction aspiration, 909 for mifepristone plus misoprostol and 832 per 1000 women for misoprostol (Summary of findings 1).

The cumulative probabilities for each method of managing a miscarriage being at each possible rank for completing a miscarriage are shown in Figure 7. Treatment hierarchies are presented with the surface under the cumulative ranking curve (SUCRA); the larger the SUCRA the higher its rank among all available methods of managing a miscarriage. Ranking indicates the cumulative probability of being the best method of managing a miscarriage, the second best, the third best, etc. A SUCRA of 100% means the method of miscarriage management is the best and a SUCRA of 0% means the method of miscarriage management is the worst. The highest ranked method for managing a miscarriage was suction aspiration plus cervical preparation (SUCRA 98.2%), followed by dilatation and curettage (SUCRA 68.2%), and suction aspiration (SUCRA 58.4%). Mifepristone plus misoprostol ranked fourth (53.2%), followed by misoprostol (SUCRA 22.1%), and expectant management or placebo (SUCRA 0%) coming last.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 7. Cumulative rankogram comparing each of the methods of management of a miscarriage for the outcome of complete miscarriage. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.

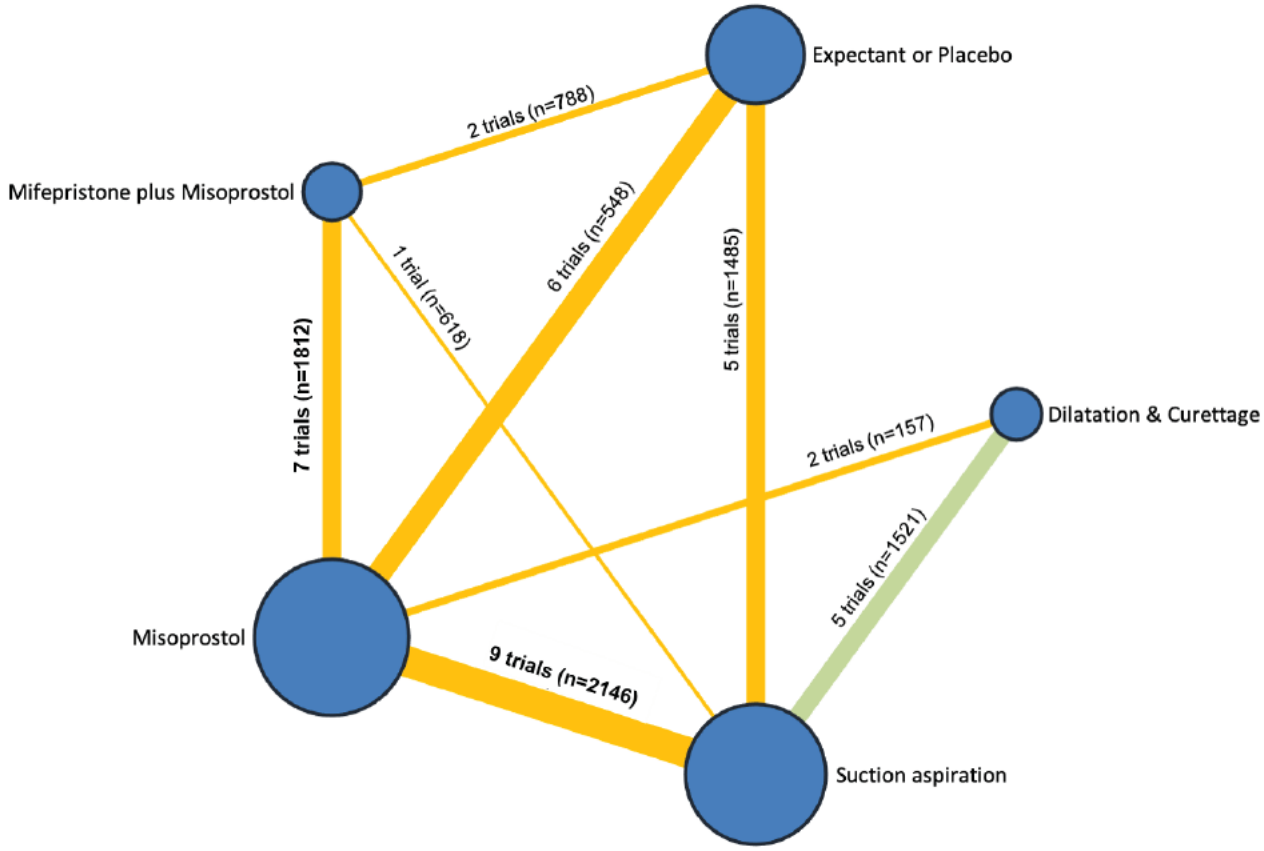


Composite outcome of death or serious complication

The network diagram for the composite outcome of death or serious complications is presented in Figure 8. Misoprostol was the most frequently investigated method of miscarriage management (24 of 37 trial arms [65%]) for this outcome (Figure 8). This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

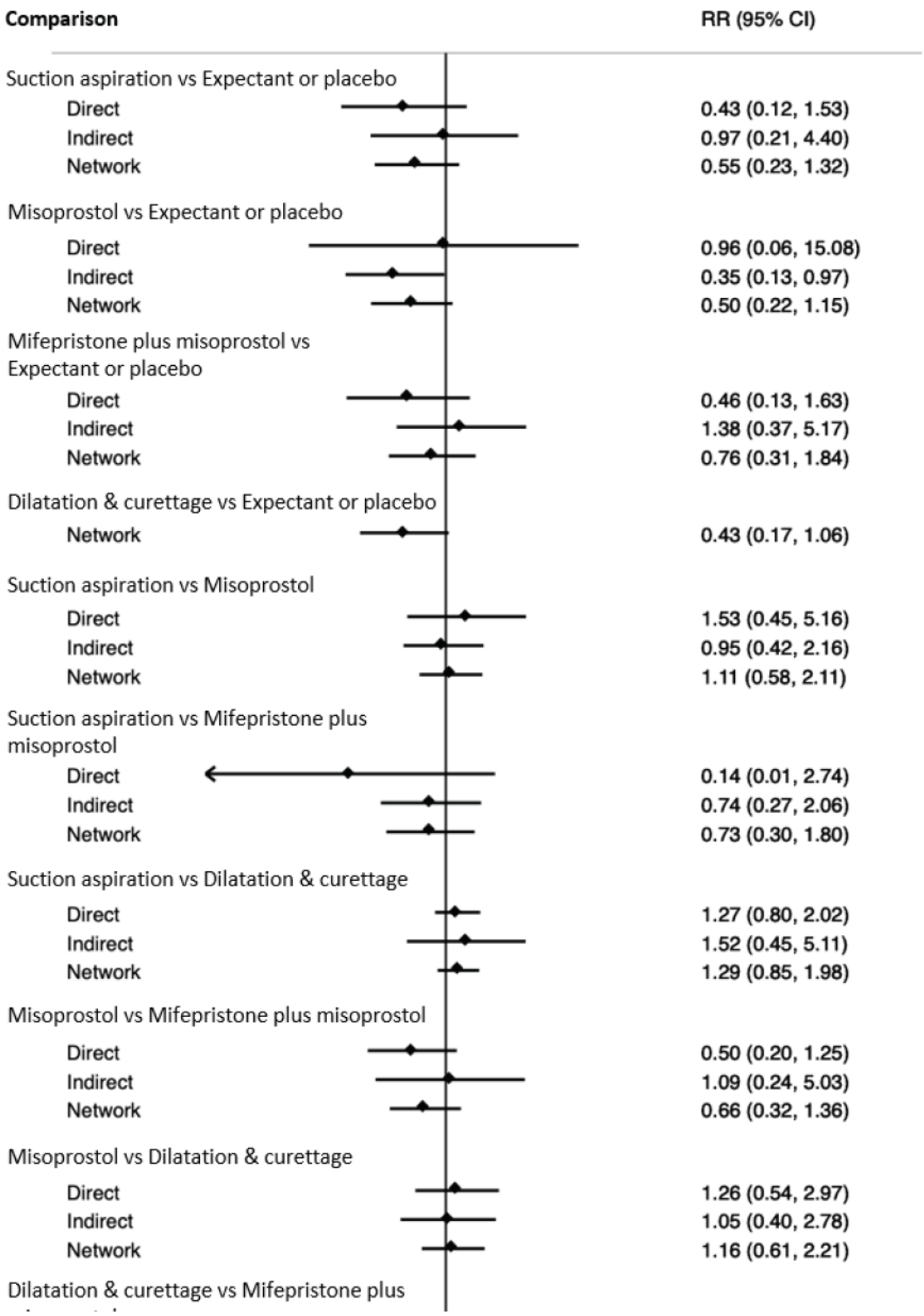
Figure 8. Network diagram for outcome of composite outcome of death or serious complication. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 35 trials suggest that dilatation and curettage (RR 0.43, 95% CI 0.17 to 1.06, *low-certainty evidence*), suction aspiration (RR 0.55, 95% CI 0.23 to 1.32, *low-certainty evidence*), misoprostol (RR 0.50, 95% CI 0.22 to 1.15, *low-certainty evidence*) and mifepristone plus misoprostol (RR 0.76, 95% CI 0.31 to 1.84, *low-certainty evidence*) were compatible with a wide range of treatment effects for death and serious complications compared with expectant management or placebo (Figure 9 Summary of findings 4).

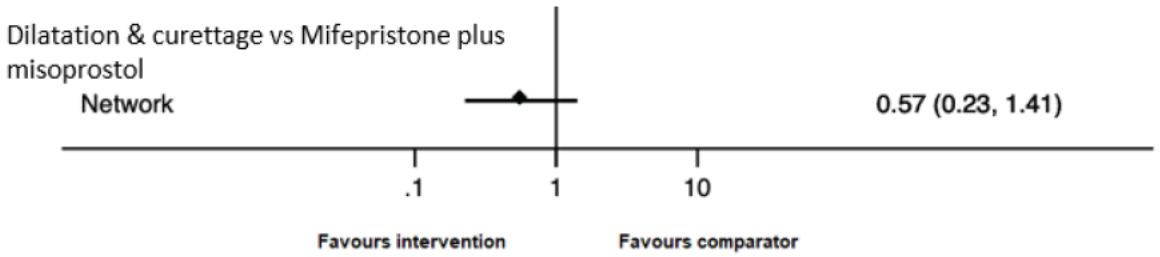
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 9. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for outcome of composite outcome of death or serious complication.



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 9. (Continued)

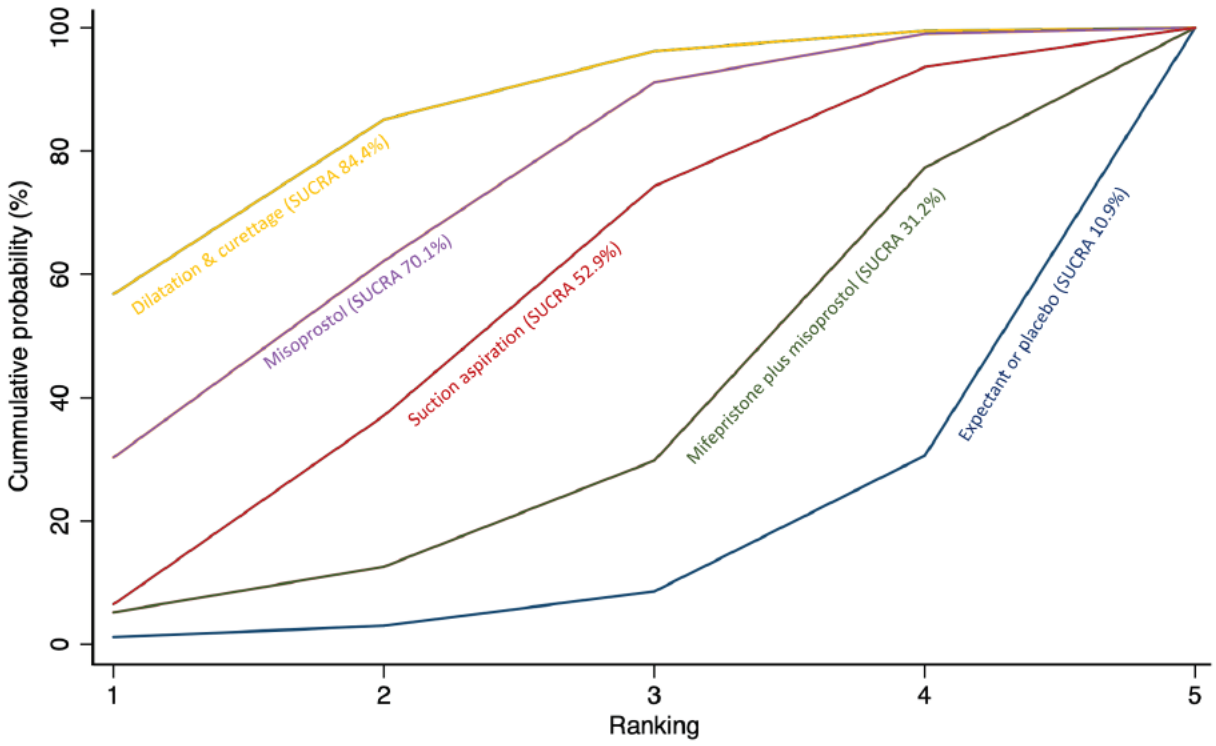


It should be noted that death was rare (no deaths across all trials were reported). The reported complications comprised mainly of blood transfusions, but also uterine perforation, need for further life-saving procedures such as hysterectomy (not including surgical completion of miscarriage as a second line intervention as this is reported in the secondary outcome of need for unplanned/emergency surgical procedure), or intensive care unit admission.

Based on these results, about 19 per 1000 women given expectant management or placebo for their miscarriage would experience death or a serious complication compared with 8 per 1000 having dilation and curettage, 10 for suction aspiration, 10 for misoprostol and 14 per 1000 for mifepristone plus misoprostol (Summary of findings 4).

The cumulative probabilities for each method of managing a miscarriage being at each possible rank for the composite outcome of death or serious complication are shown in Figure 10. The highest ranked method for managing a miscarriage for the composite outcome of death or serious complication was dilatation and curettage (SUCRA 84.4%), followed by misoprostol (SUCRA 70.1%), suction aspiration (SUCRA 52.9%), with mifepristone plus misoprostol (SUCRA 31.2%) ranked fourth and expectant management or placebo (SUCRA 10.9%) last.

Figure 10. Cumulative rankogram comparing each of the methods of management of a miscarriage for the outcome of composite outcome of death or serious complication. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.



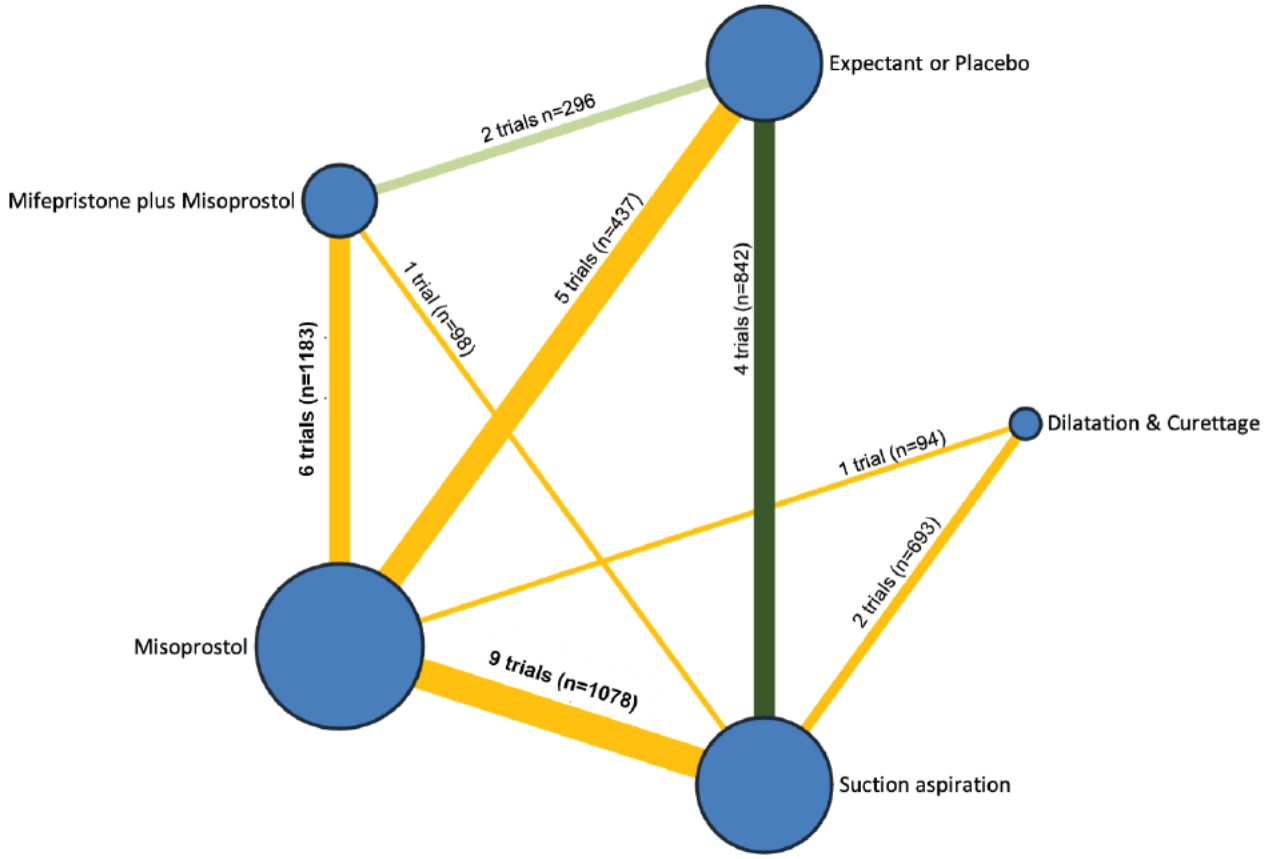
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Secondary Outcomes

Need for unplanned/emergency surgical procedure

The network diagram for the outcome of need for unplanned/ emergency surgical procedure is presented in Figure 11. 30 trial arms contributed towards this outcome. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

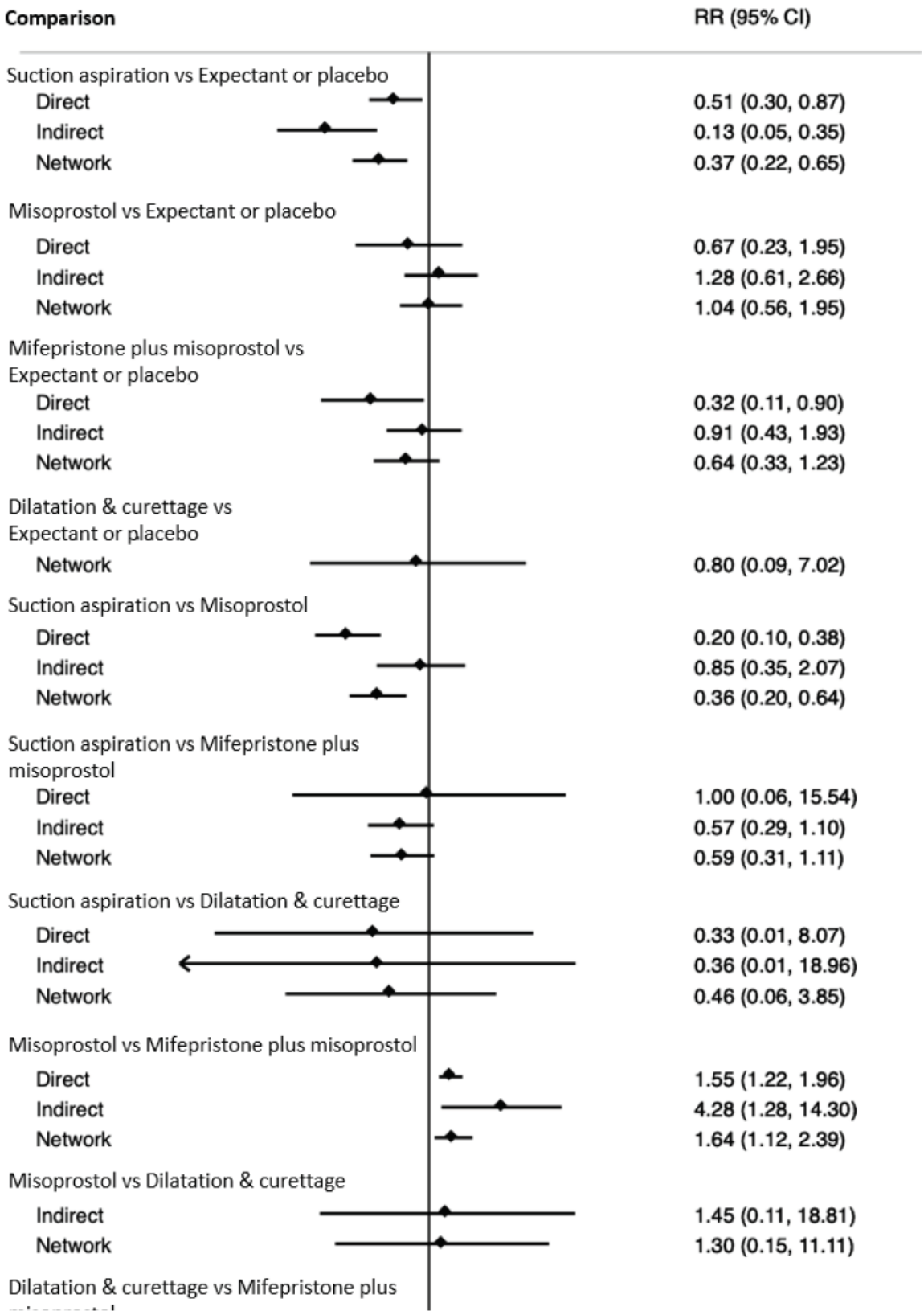
Figure 11. Network diagram for outcome of need for unplanned/ emergency surgical procedure. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 28 trials, suggest that suction aspiration (RR 0.37, 95% CI 0.22 to 0.65, *moderate-certainty evidence*) probably reduces the need for unplanned/ emergency surgical procedures when compared with expectant management or placebo. For mifepristone plus misoprostol (RR 0.64, 95% CI 0.33 to 1.23, *low-certainty evidence*) we cannot rule out an important benefit for this outcome. For dilatation and curettage (RR 0.80, 95% CI 0.09 to 7.02, *very low-certainty evidence*) and misoprostol (RR 1.04, 95% CI 0.56 to 1.95, l*ow-certainty evidence*), results are compatible with a wide range of treatment effects (Figure 12, Summary of findings 5).

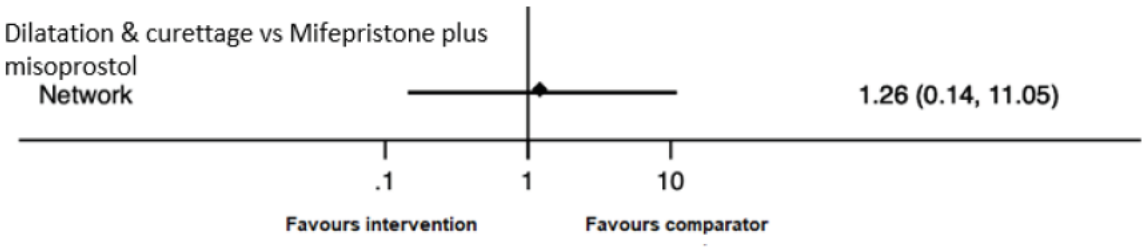
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 12. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for outcome of need for unplanned/ emergency surgical procedure.



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

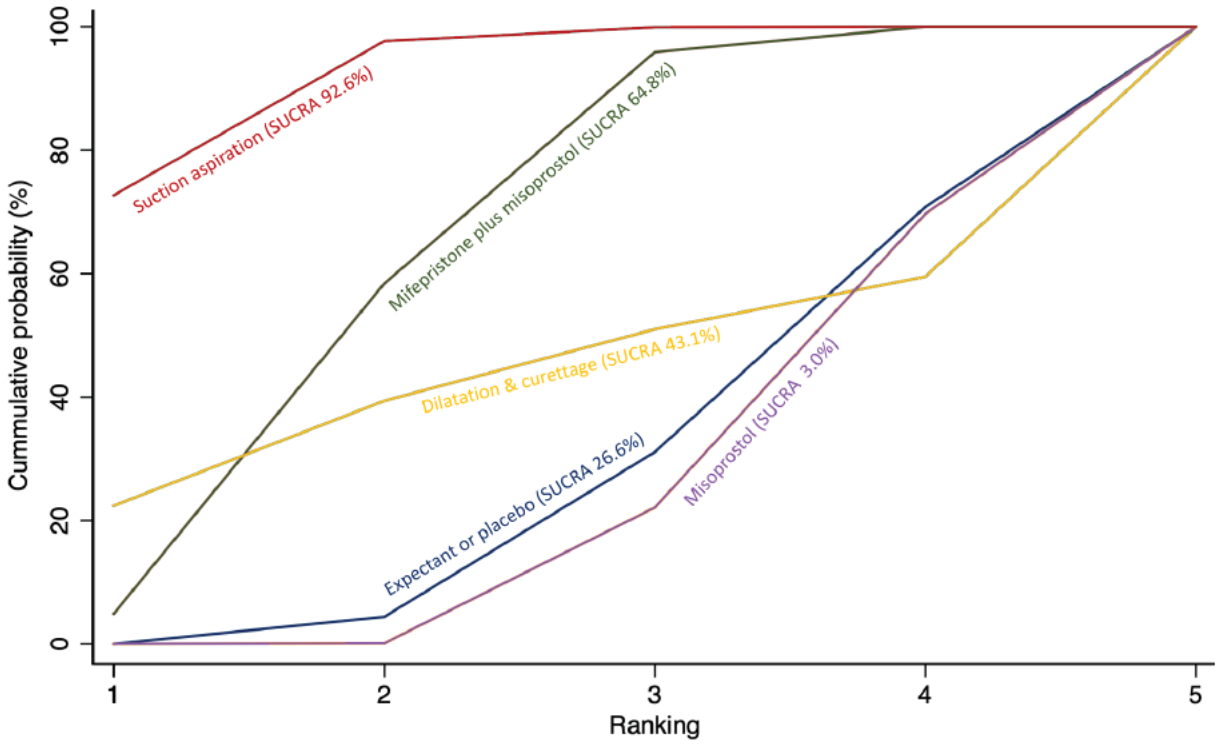
Figure 12. (Continued)



Based on these results, about 120 per 1000 women given expectant management or placebo for their miscarriage would experience unplanned or emergency surgical procedures compared with 44 per 1000 women for suction aspiration, 77 for mifepristone plus misoprostol, 96 for dilatation and curettage and 125 per 1000 women having for misoprostol (Summary of findings 5).

The cumulative probabilities for each method of managing a miscarriage being at each possible rank for the need for unplanned/ emergency surgical procedure are shown in Figure 13. The highest ranked method for managing a miscarriage was suction aspiration (SUCRA 92.6%), followed by mifepristone plus misoprostol (SUCRA 64.8%), with dilatation and curettage (SUCRA 43.1%) ranked third, expectant management or placebo (SUCRA 26.6%) fourth and misoprostol (SUCRA 3.0%) last.

Figure 13. Cumulative rankogram comparing each of the methods of management of a miscarriage for the outcome of need for unplanned/ emergency surgical procedure. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.

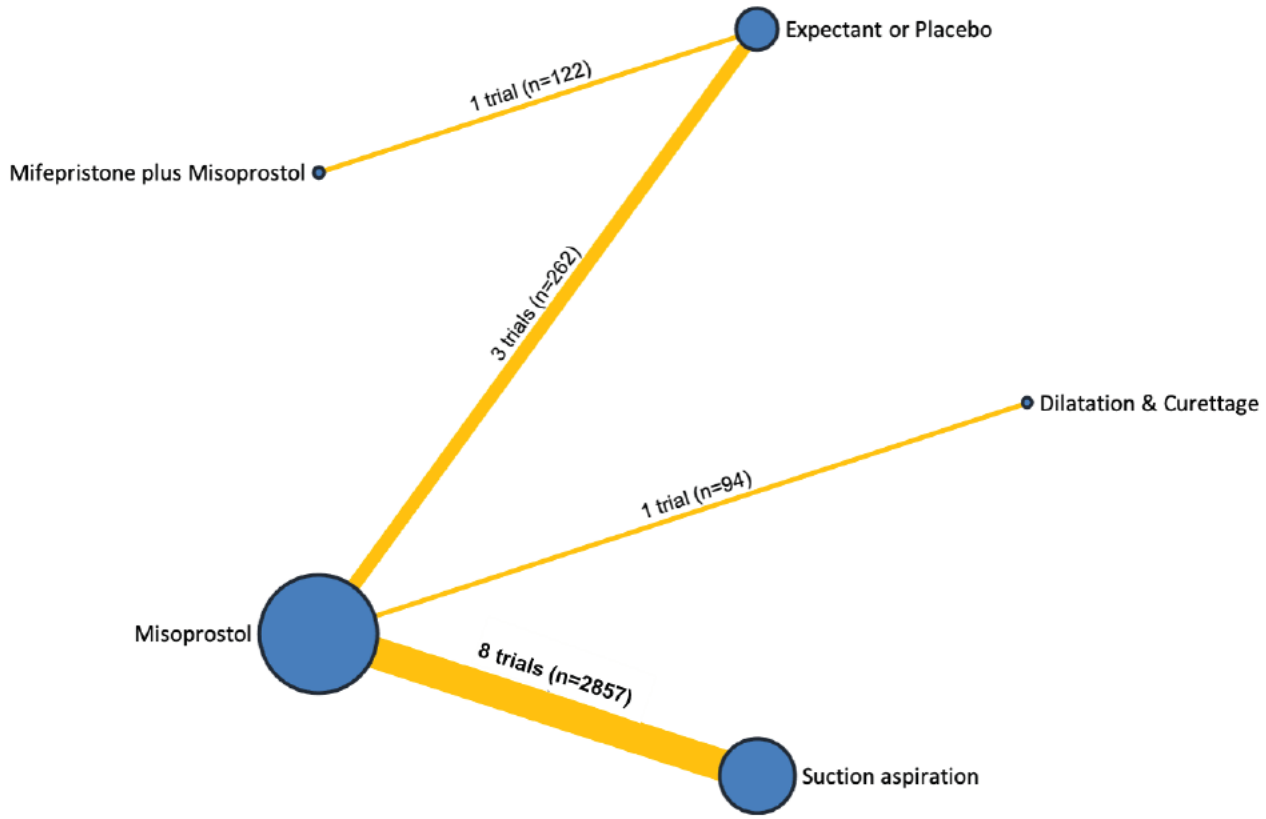


Pain scores (visual analogue scale)

The network diagram for the outcome of pain scores (visual analogue scale) is presented in Figure 14. 13 trials contributed towards this outcome. This outcome was not reported for any trial involving suction curettage plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 14. Network diagram for outcome of pain score (visual analogue scale). 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 and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Due to the small number of trials reporting this outcome, network meta-analysis was not possible, and so were unable to produce network relative effects and a rankogram. Direct evidence is presented only from pairwise meta-analysis (Data and analyses).

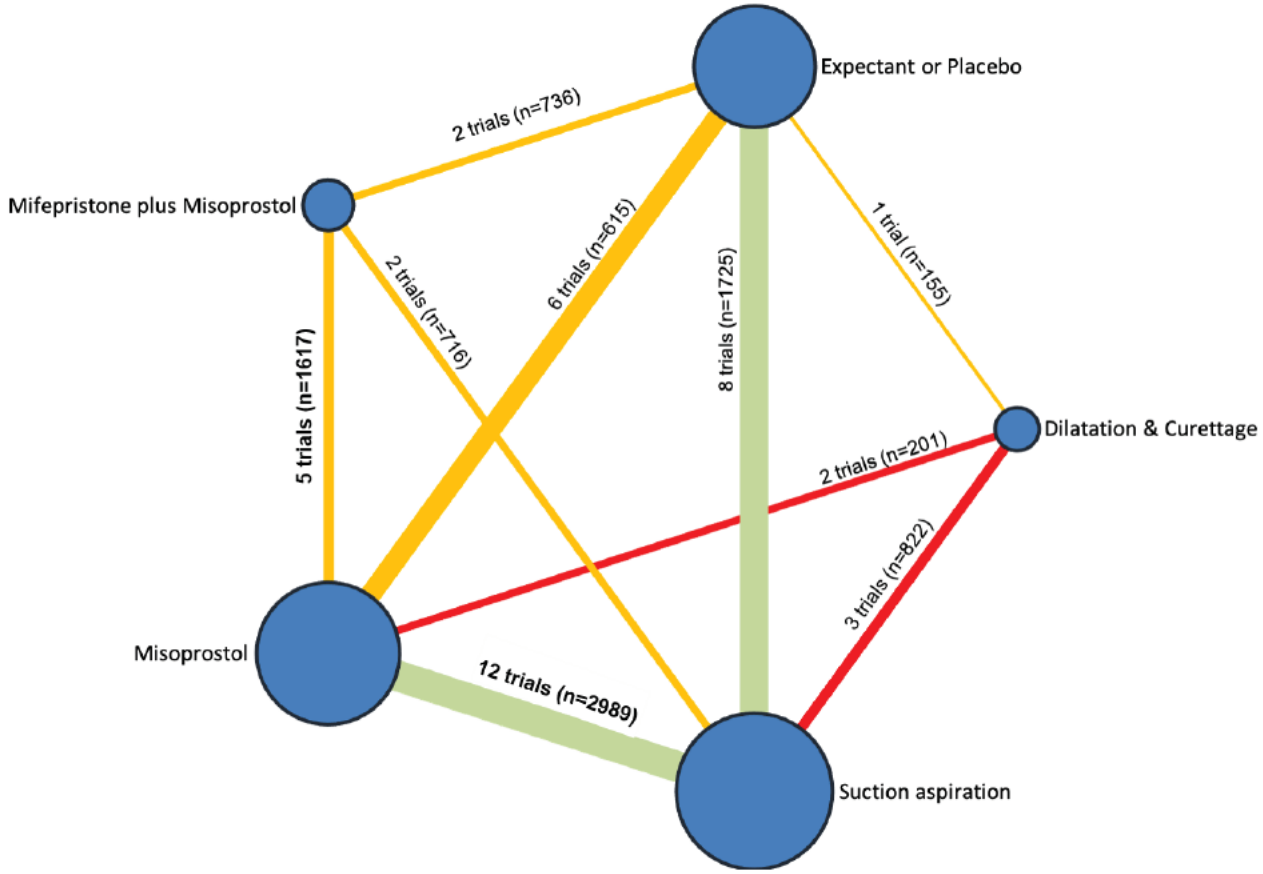
Pairwise meta-analysis of three trials found misoprostol may cause a slightly higher pain score compared to expectant management or placebo (standardised mean difference (SMD) 0.33, 95% CI 0.08 to 0.57, *low-certainty evidence*) (Analysis 8.4). One further trial compared mifepristone plus misoprostol to expectant management or placebo but we cannot rule out a small difference in pain scores for this comparison (SMD 0.14, 95% CI -0.21 to 0.50, *low-certainty evidence*) (Analysis 10.4).

Pelvic Inflammatory disease, sepsis or endometritis

The network diagram for the outcome of pelvic inflammatory disease, sepsis or endometritis is presented in Figure 15. 41 trial arms contributed towards this outcome. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

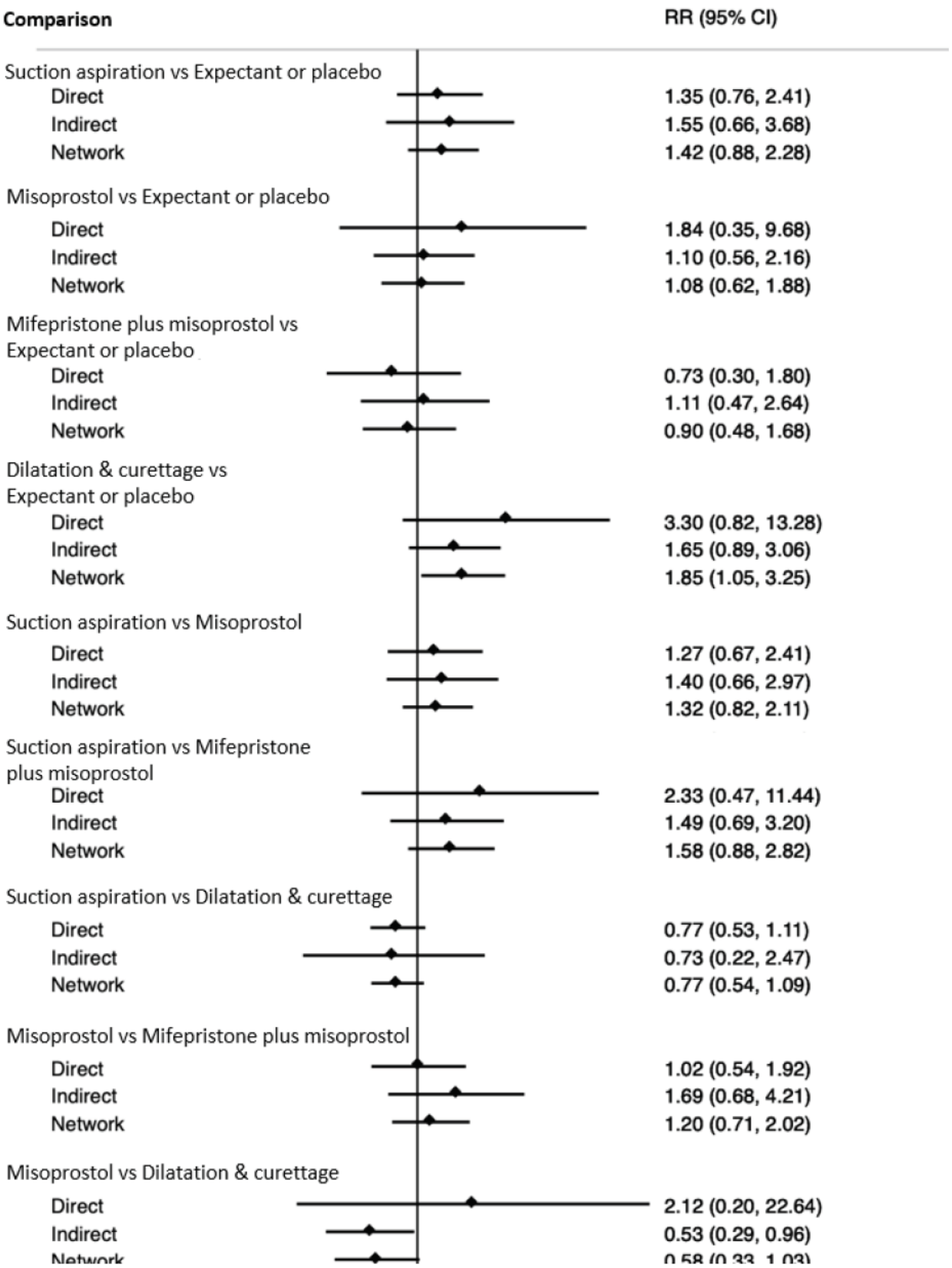
Figure 15. Network diagram for outcome of pelvic inflammatory disease, sepsis or endometritis. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 39 trials, suggest that mifepristone plus misoprostol (RR 0.90, 95% CI 0.48 to 1.68, *low-certainty evidence*), misoprostol (RR 1.08, 95% CI 0.62 to 1.88, *moderate-certainty evidence*) and suction aspiration (RR 1.42, 95% CI 0.88 to 2.28, *moderate-certainty evidence*) were compatible with a wide range of treatment effects for pelvic inflammatory disease, sepsis or endometritis when compared with expectant management or placebo. However, dilatation and curettage (RR 1.85, 95% CI 1.05 to 3.25, *very low-certainty evidence*) may increase the risk of pelvic inflammatory disease, sepsis or endometritis when compared with expectant management or placebo, but the evidence is very uncertain (Figure 16, Summary of findings 7).

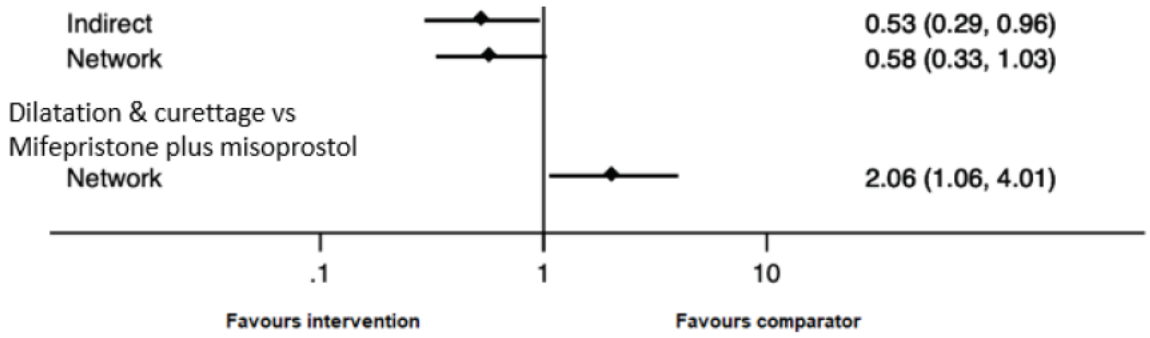
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 16. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for outcome of pelvic inflammatory disease, sepsis or endometritis.



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

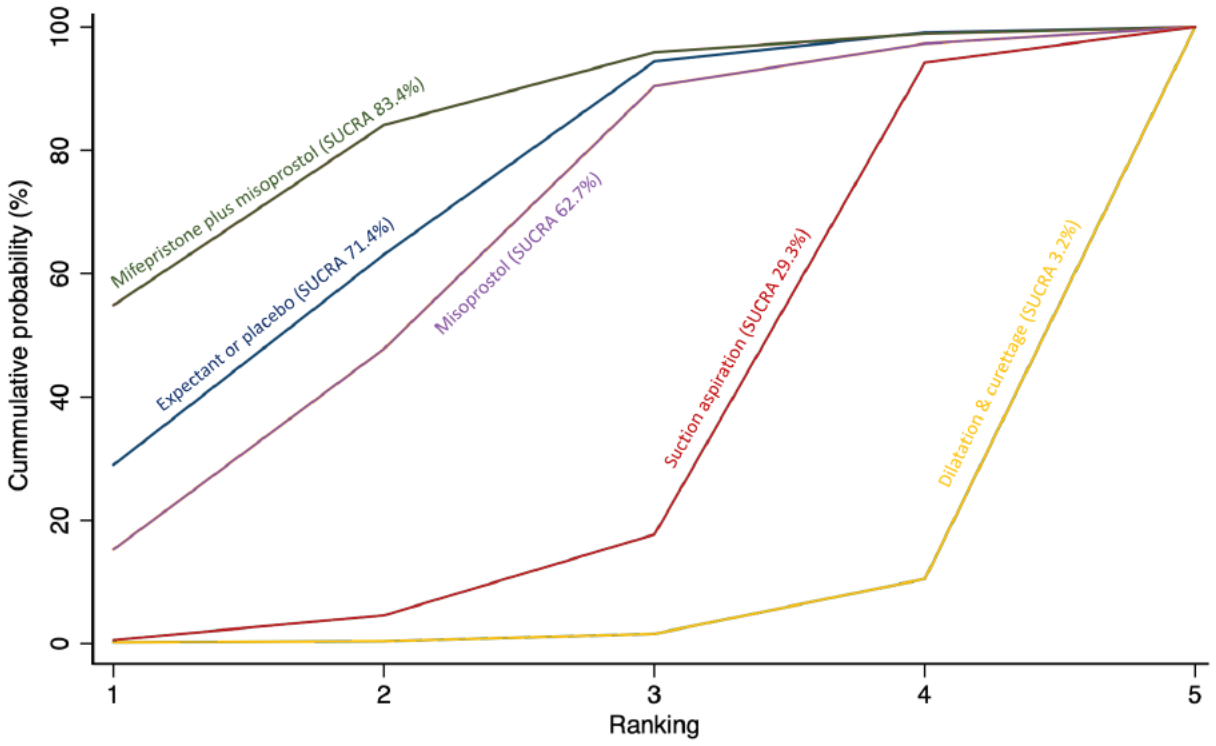
Figure 16. (Continued)



Based on these results, about 36 per 1000 women given expectant management or placebo for their miscarriage would experience pelvic inflammatory disease, sepsis or endometritis compared with 32 per 1000 women for mifepristone plus misoprostol, 39 for misoprostol, 51 for suction aspiration, and 67 per 1000 women having dilatation and curettage (Summary of findings 7).

The cumulative probabilities for each method of managing a miscarriage being at each possible rank for pelvic inflammatory disease, sepsis or endometritis are shown in Figure 17. The highest ranked method for managing a miscarriage for the outcome of pelvic inflammatory disease, sepsis or endometritis was mifepristone plus misoprostol (SUCRA 83.4%), followed by expectant management or placebo (SUCRA 71.4%), misoprostol (SUCRA 62.7%), with suction aspiration (SUCRA 29.3%) ranked fourth and dilatation and curettage (SUCRA 3.2%) last.

Figure 17. Cumulative rankogram comparing each of the methods of management of a miscarriage for the outcome of pelvic inflammatory disease, sepsis or endometritis. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.

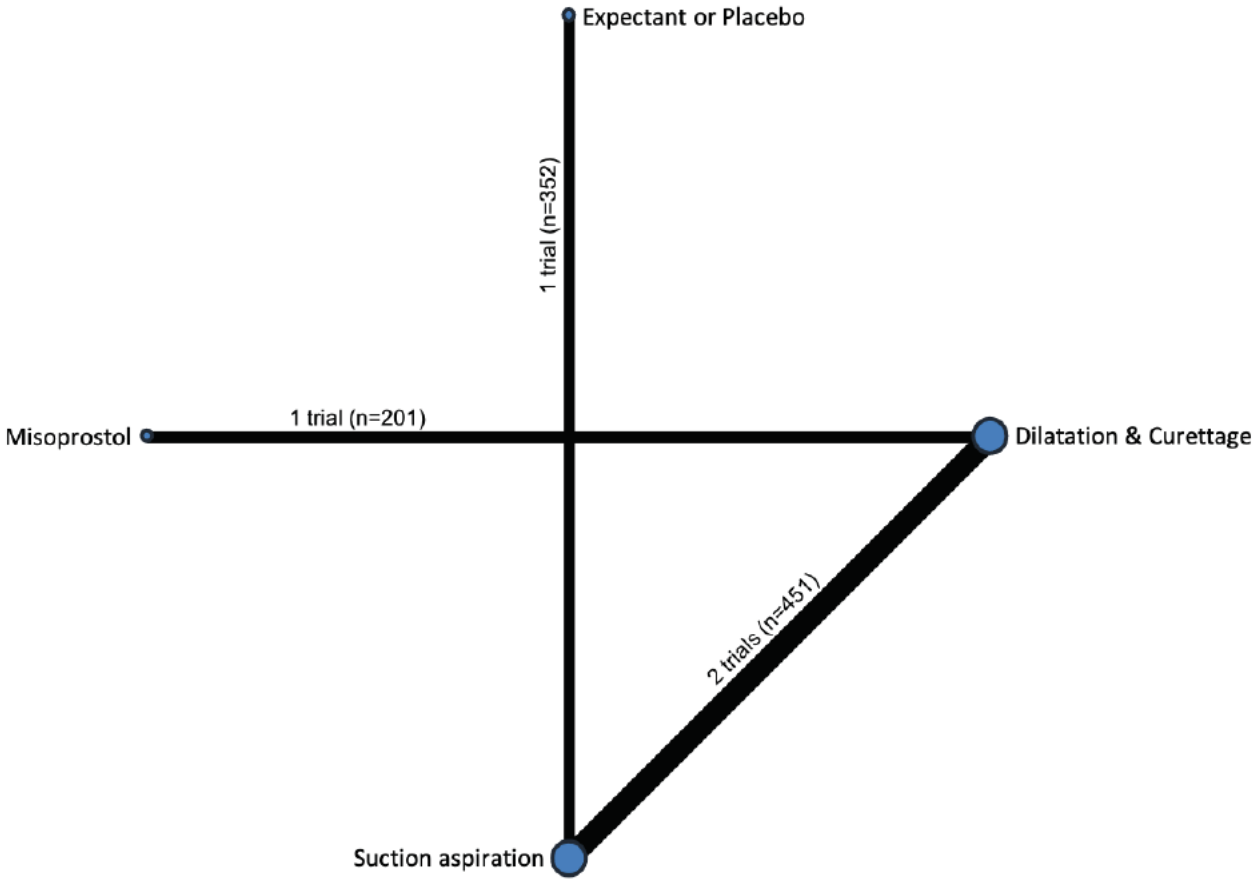


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Mean volumes of blood loss (millilitres (mL)

The network diagram for the outcome of mean volumes of blood loss (mL) is presented in Figure 18. Four trials contributed towards this outcome. This outcome was not reported for any trial involving suction aspiration plus cervical preparation. Due to the small number of trials reporting this outcome, we were unable to produce network relative effects and a rankogram. Direct evidence is presented only from pairwise meta-analysis. One trial found suction aspiration may cause smaller volumes of blood loss compared to expectant management or placebo (mean difference (MD) -23.00, 95% CI -40.41 to -5.59).

Figure 18. Network diagram for outcome of mean volumes of blood loss (millilitres). 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 and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. Multi-arm trials contribute to more than one comparison.

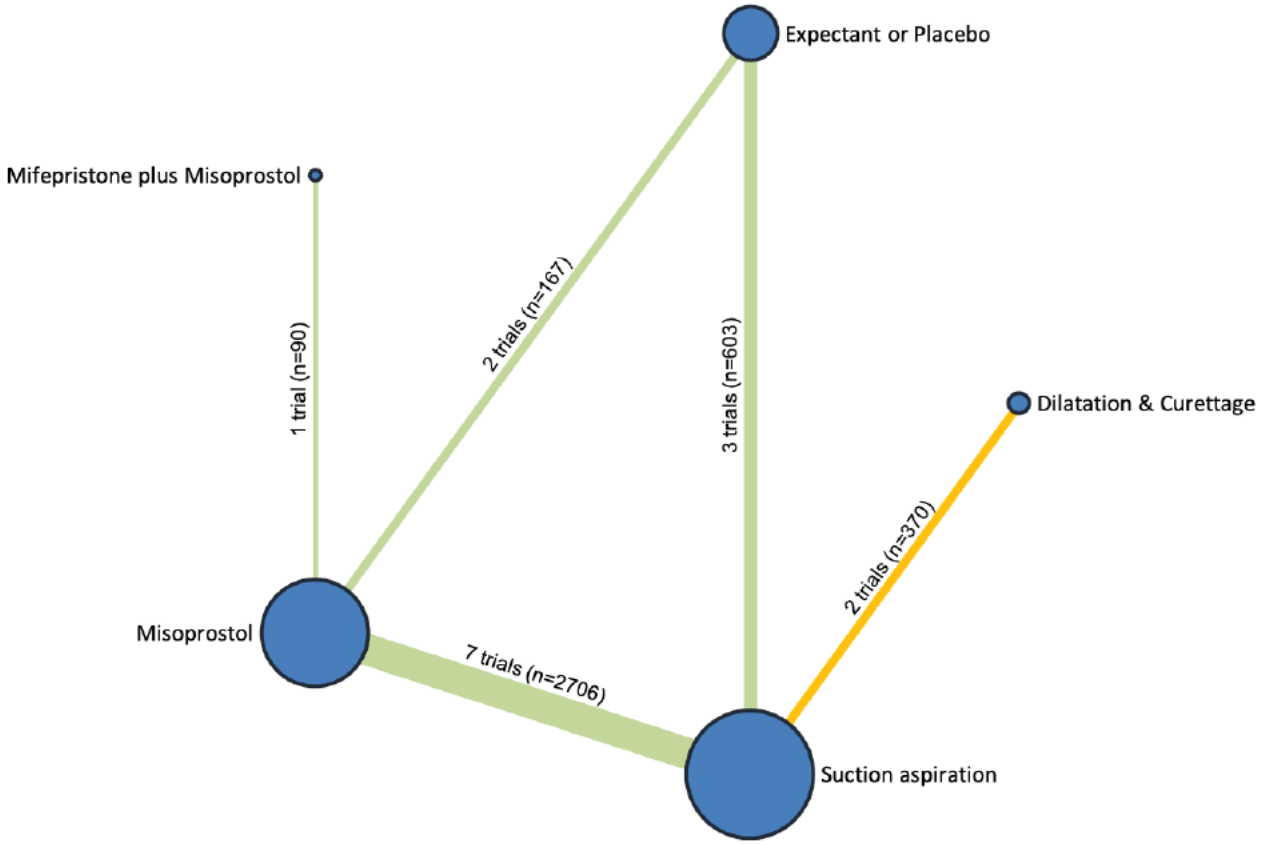


Change in haemoglobin measurements before and after the miscarriage

The network diagram for the outcome of change in haemoglobin measurements before and after the miscarriage is presented in Figure 19. 15 trial arms contributed towards this outcome. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

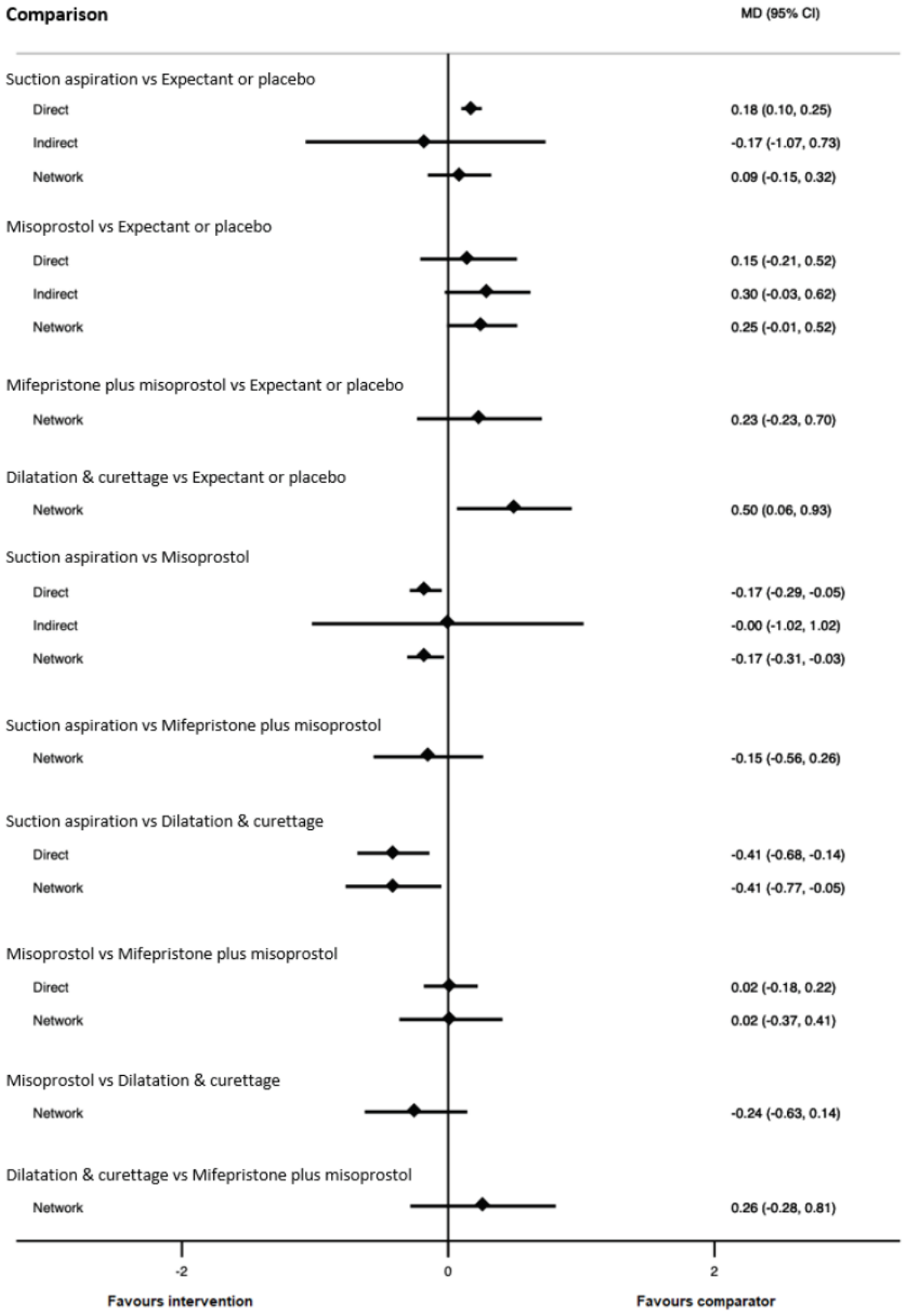
Figure 19. Network diagram for outcome of change in haemoglobin measurements before and after the miscarriage. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 13 trials, suggest that dilatation and curettage (MD 0.50, 95% CI 0.06 to 0.93, *low-certainty evidence*) may cause a change in haemoglobin measurement before and after the miscarriage when compared with expectant management or placebo. Misoprostol (MD 0.25, 95% CI -0.01 to 0.52, *low-certainty evidence*) and mifepristone plus misoprostol (MD 0.23, 95% CI -0.23 to 0.70, *moderate-certainty evidence*) may make little or no difference to this outcome when compared to expectant management or placebo. Suction aspiration (MD 0.09, 95% CI -0.15 to 0.32, *very low-certainty evidence*) makes little or no difference to this outcome when compared with expectant management or placebo, but the evidence is very uncertain (Figure 20).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 20. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for outcome of change in haemoglobin measurements before and after the miscarriage.



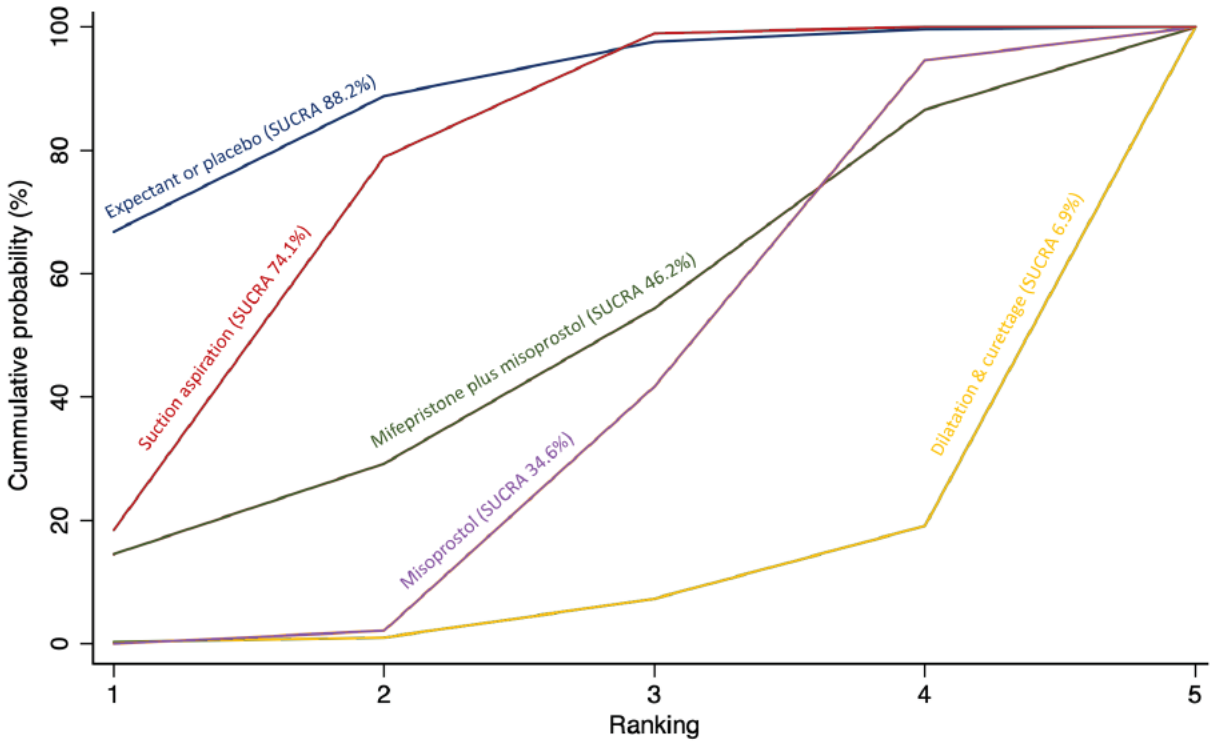
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 20. (Continued)

Favours intervention | Favours comparator

The cumulative probabilities for each method of managing a miscarriage being at each possible rank for the outcome of change in haemoglobin measurements before and after the miscarriage are shown in Figure 21. The highest ranked method for managing a miscarriage for the outcome of change in haemoglobin measurements before and after the miscarriage was expectant management or placebo (SUCRA 88.2%), followed by suction aspiration (SUCRA 74.1%), mifepristone plus misoprostol (SUCRA 46.2%), with misoprostol (SUCRA 34.6%) ranked fourth and dilatation and curettage (SUCRA 6.9%) last.

Figure 21. Cumulative rankogram comparing each of the methods of management of a miscarriage for the outcome of change in haemoglobin measurements before and after the miscarriage. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.

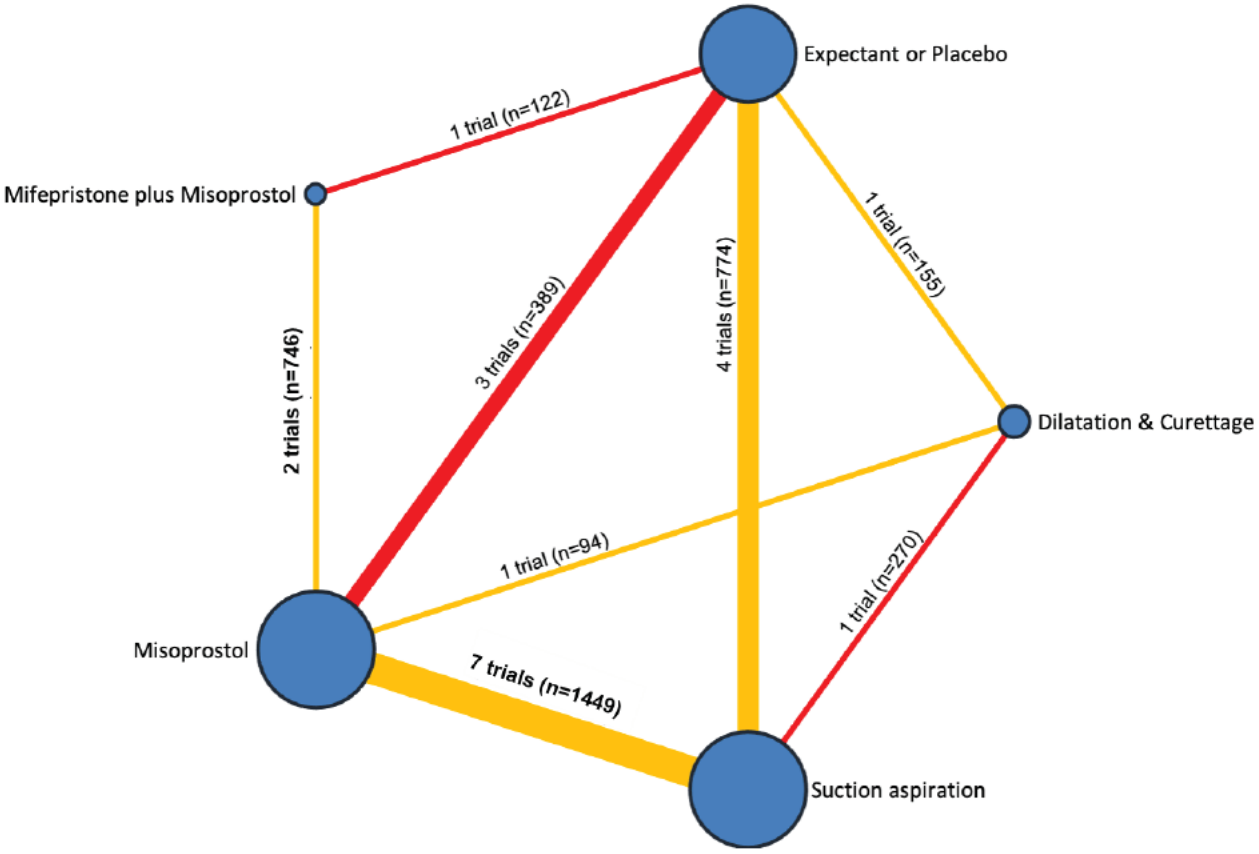


Days of bleeding

The network diagram for the outcome of days of bleeding is presented in Figure 22. 20 trial arms contributed towards this outcome. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

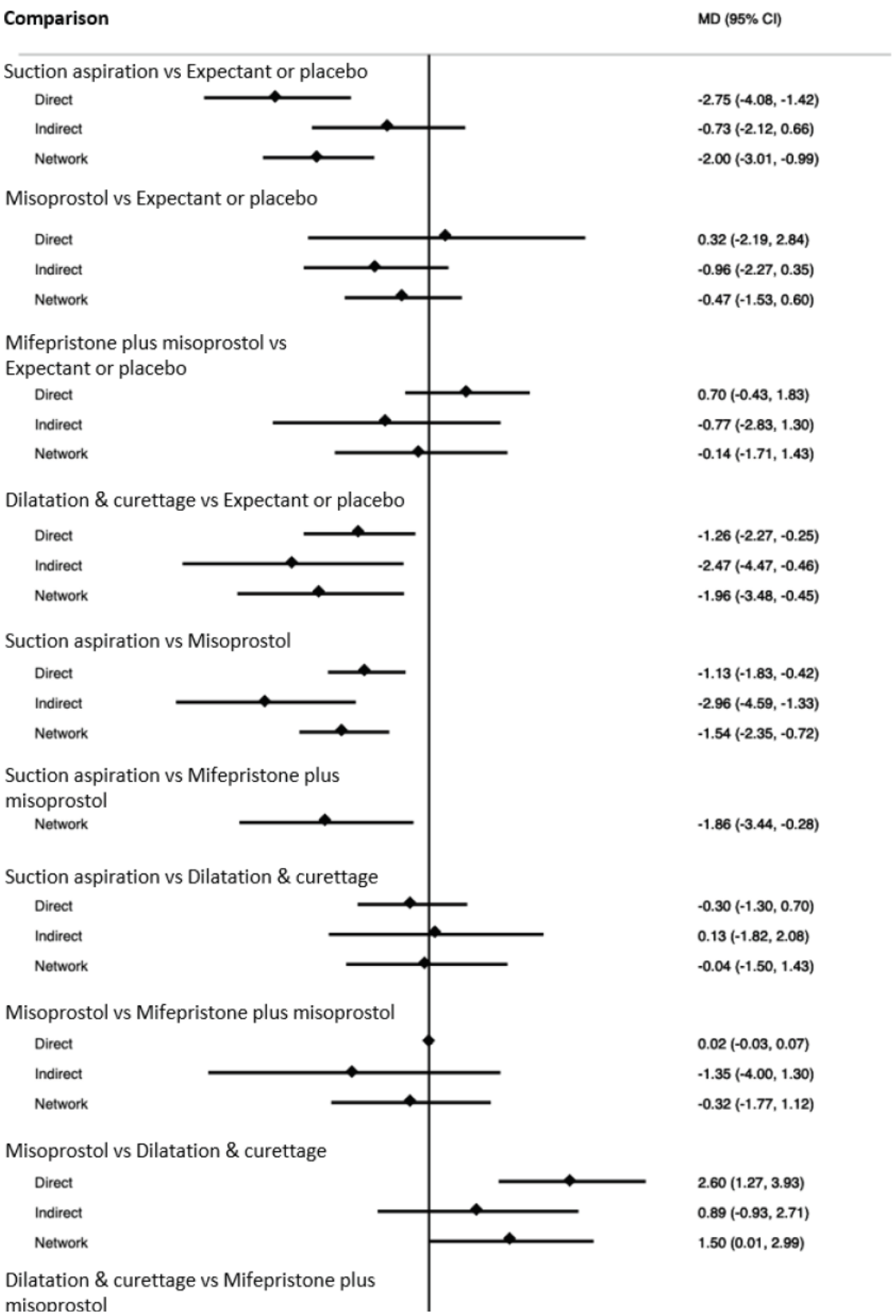
Figure 22. Network diagram for outcome of days of bleeding. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 18 trials suggest that dilatation and curettage (MD -1.96, 95% CI -3.48 to -0.45, *low-certainty evidence*) may cause less days of bleeding when compared with expectant management or placebo. Suction aspiration (MD -2.00, 95% CI -3.01 to -0.99, *very low-certainty evidence*) may cause less days of bleeding when compared to expectant management or placebo, but the evidence is very uncertain. Misoprostol (MD -0.47, 95% CI -1.53 to 0.60, *very low-certainty evidence*) and mifepristone plus misoprostol (MD -0.14, 95% CI -1.71 to 1.43, *very low-certainty evidence*), were compatible with a wide range of treatment effects for days of bleeding when compared to expectant management or placebo (Figure 23, Summary of findings 8).

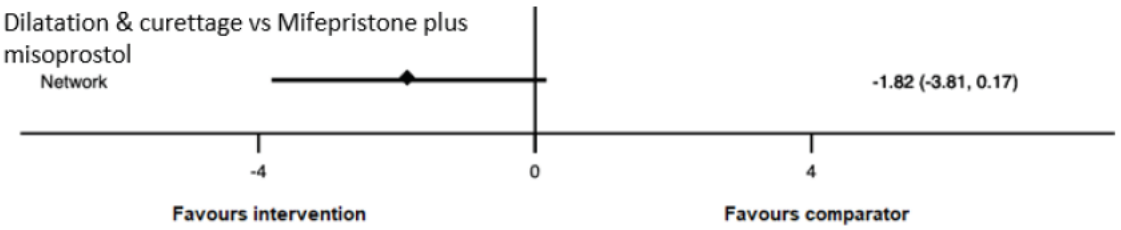
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 23. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for outcome of days of bleeding.



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

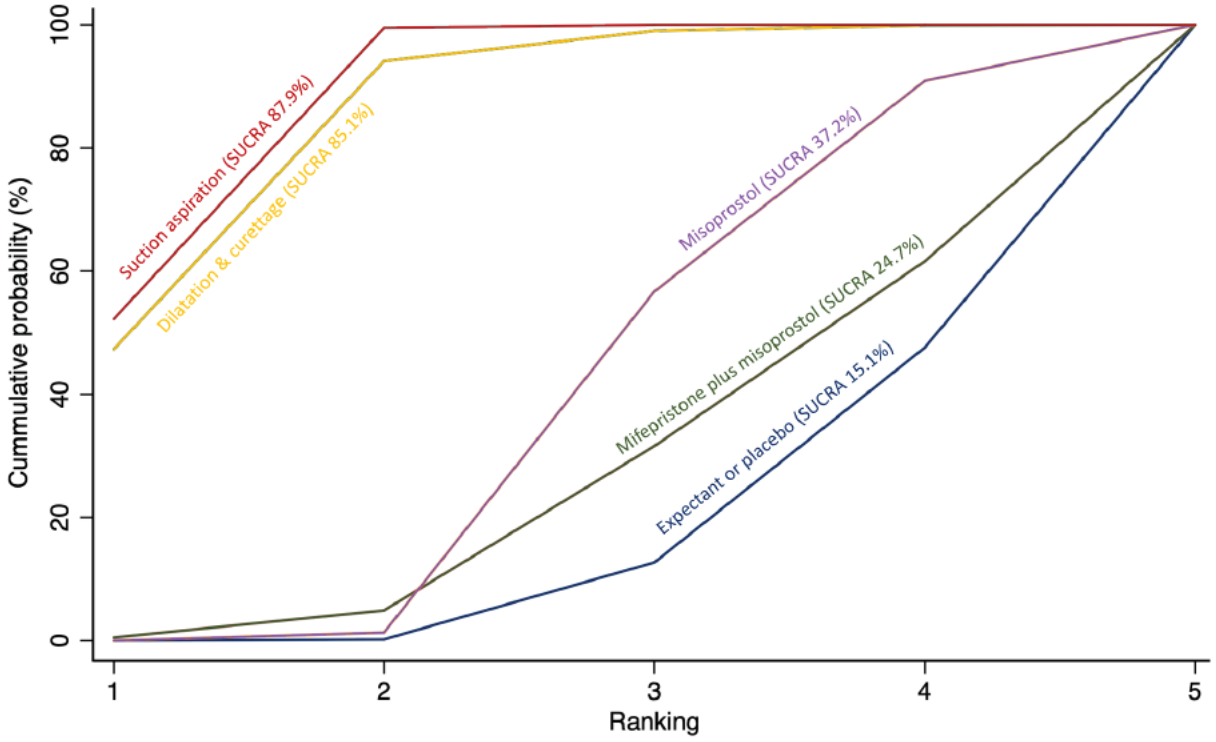
Figure 23. (Continued)



Based on these results, women given expectant management or placebo for their miscarriage, would experience 10 days of bleeding compared with 8 days of bleeding for women having suction aspiration, 8.04 days for women having dilatation and curettage, 9.53 days for women having misoprostol and 9.86 days of bleeding for women having mifepristone plus misoprostol (Summary of findings 8).

The cumulative probabilities for each method of managing a miscarriage being at each possible rank for the outcome of days of bleeding are shown in Figure 24. The highest ranked method for managing a miscarriage for the outcome of days of bleeding was suction aspiration (SUCRA 87.9%), followed by dilatation and curettage (SUCRA 85.1%), misoprostol (SUCRA 37.2%) with mifepristone plus misoprostol (SUCRA 24.7%) ranked fourth and expectant management or placebo (SUCRA 15.1%) last.

Figure 24. Cumulative rankogram comparing each of the methods of management of a miscarriage for the outcome of days of bleeding. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.



Cervical Tear

Due to the infrequency at which cervical tears occurred across all studies where it was reported, we were unable to produce a network diagram, network relative effects and a rankogram. Direct evidence is presented only from pairwise meta-analysis. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Only eight trials reported this outcome with five reporting no cervical tears for either intervention it was comparing. The most frequently investigated intervention for this outcome was suction aspiration with seven trials out of eight. Pairwise meta-analysis suggests that we cannot rule out a substantial harm of suction aspiration compared with misoprostol (3 trials, RR 7.18, 95% CI 0.84 to 61) and substantial benefit for suction aspiration compared with dilatation and curettage (2 trials, RR 0.49, 95% CI 0.20 to 1.18) (Analysis 3.8).

Women's views or satisfaction

There was significant heterogeneity in the methods of reporting women's views or satisfaction across all the studies where it was reported and so we were unable to produce a network diagram, network relative effects and a rankogram. Direct meta-analysis was also not possible and so results are presented narratively. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Twenty-three trials reported women's views or satisfaction using varying different methods. Four trials (Bagratee 2004; Moodliar 2005; Nielsen 1999; Phusaanantakul 2010) used a visual analogue scale. Eight trials used a five-point descriptive scale (very satisfied, satisfied, neutral, dissatisfied and very dissatisfied) (Bique 2007; Chigbu 2012; Dabash 2010; Dao 2007; Montesinos 2011; Shwekerela 2007; Taylor 2011; Weeks 2005), and seven trials used a three-point descriptive scale (satisfied, neutral and dissatisfied) (Chipchase 1997; Dangalla 2012; Demetroulis 2001; Ibiyemi 2018; Lister 2005; Niinimaki 2006; Shuaib 2013.

Overall, all methods of managing a miscarriage were found to be acceptable. The most commonly investigated method of miscarriage management was misoprostol with 18 trials, followed by suction aspiration with 17 trials. The most common comparison was misoprostol versus suction aspiration with 12 trials. Of these 12 trials, Arellano 2009 examined only the side effects of the treatment options with 95% describing the side effects of misoprostol as tolerable, whereas 91% described the side effects of suction aspiration as tolerable. Sahin 2001 described women's dissatisfaction with only one woman out of 40 being dissatisfied with misoprostol, whereas 14 women out of 40 were dissatisfied with suction aspiration. The remaining 10 trials used either a five- or three-point scale of satisfaction. In total, 1389 women out of 1443 (96.3%) were either satisfied or very satisfied with misoprostol and 1350 women out of 1400 (96.4%) were either satisfied or very satisfied with suction aspiration.

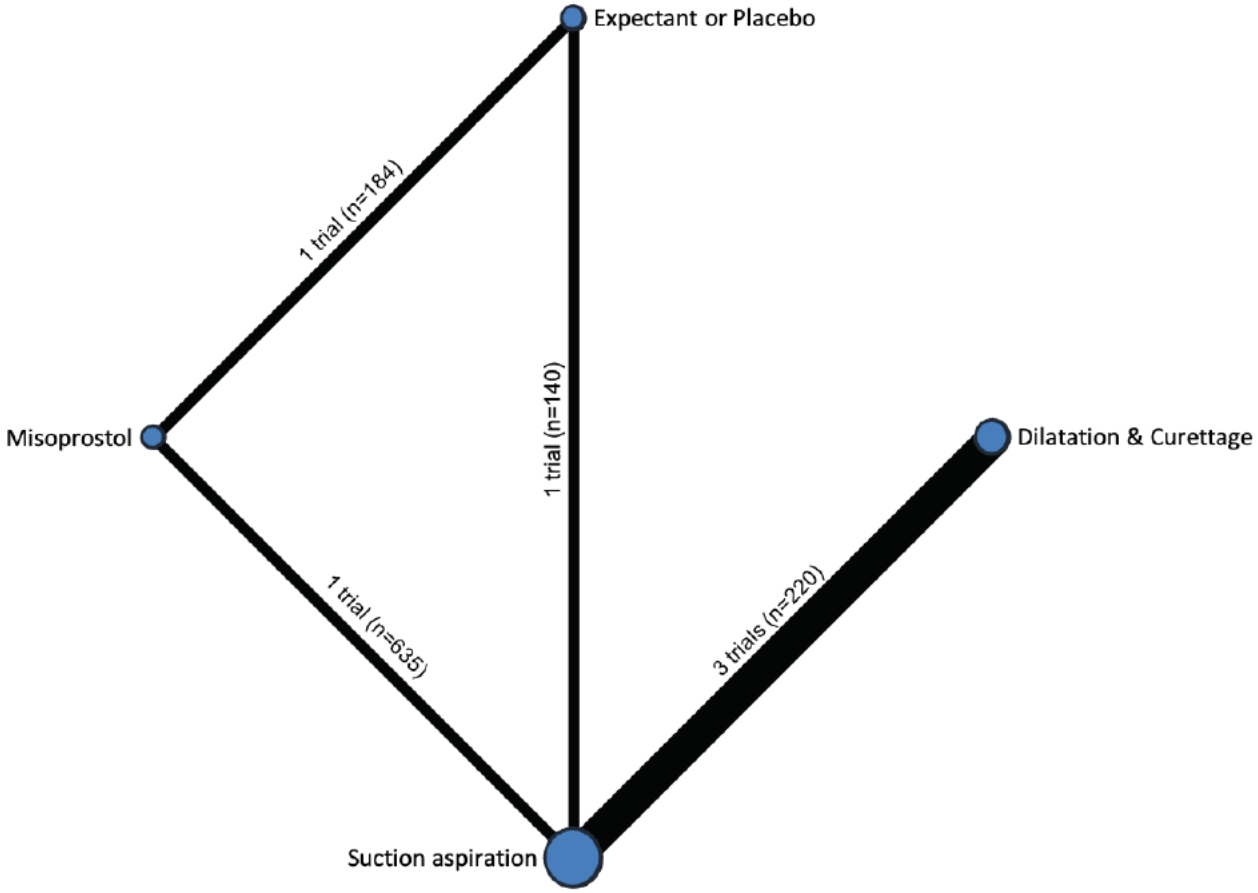
Suction aspiration versus expectant management or placebo was the next most common comparison with three trials. Chipchase 1997; and Dangalla 2012 found 92 out of 96 women (98.5%) were satisfied with suction aspiration compared to 97 out of 99 women (98.0%) were satisfied with expectant management or placebo (*moderate-certainty evidence*). Nadarajah 2014 used a 10-point numerical scale and similarly found suction aspiration had a satisfaction score of 7.57 from 175 women and expectant management or placebo also had a 7.57 score from 177 women (*moderate-certainty evidence*). Two trials compared misoprostol versus expectant/placebo and misoprostol versus dilatation and curettage respectively (Summary of findings 9).

Mean duration of hospital stay (days)

The network diagram for the outcome of mean duration of hospital stay (days) is presented in Figure 25. Six trials contributed towards this outcome. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 25. Network diagram for outcome of mean duration of hospital stay (days). 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 and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. Multi-arm trials contribute to more than one comparison.



Due to the small number of trials reporting this outcome, network meta-analysis was not possible for this outcome, and so we were unable to produce a network diagram, network relative effects and a rankogram. Direct evidence is presented only from pairwise meta-analysis.

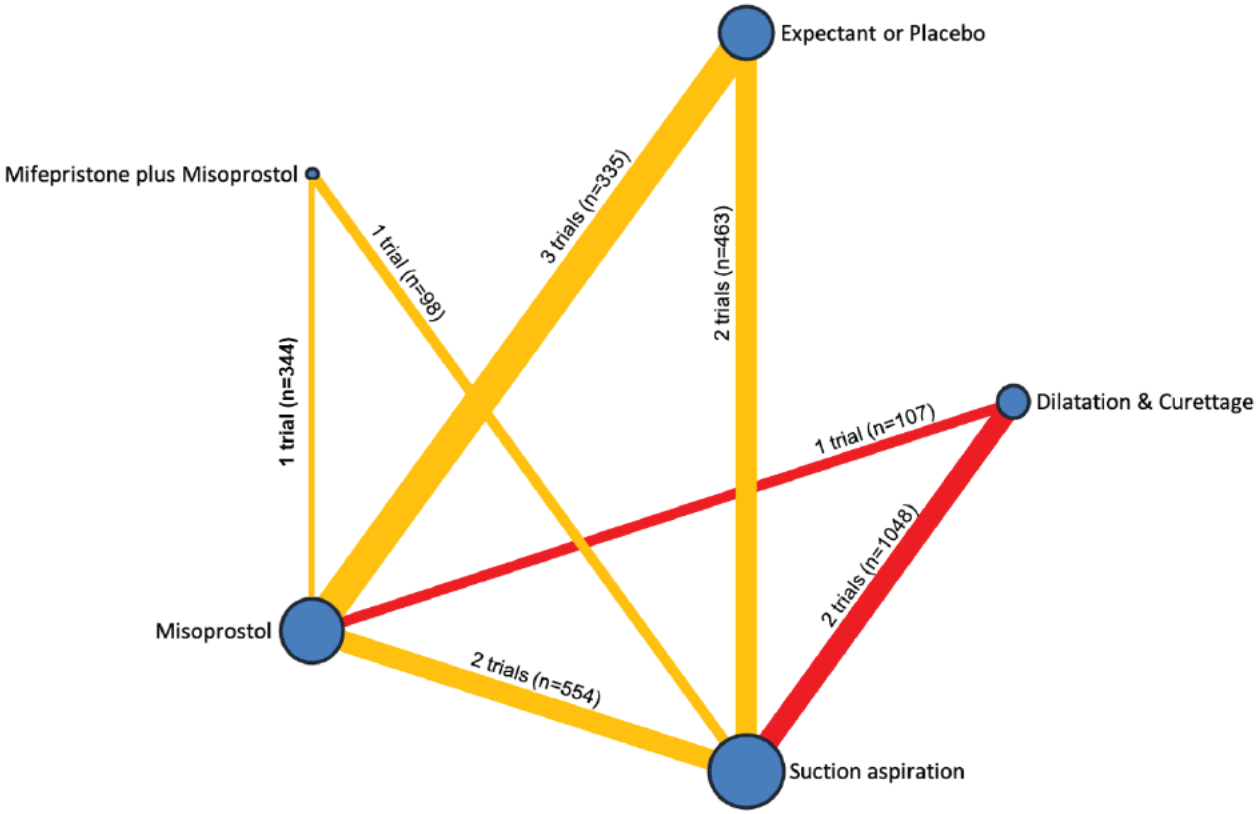
Pairwise meta-analysis of three trials suggests women having suction aspiration probably have a shorter mean duration of hospital stay when compared to dilatation and curettage (MD -0.56, 95% CI -0.89 to -0.23) (Analysis 3.9). One trial shows women having suction aspiration probably have a shorter mean duration of hospital stay when compared to misoprostol (MD -0.40, 95% CI -0.68 to -0.12) (Analysis 1.9). Misoprostol may have a shorter mean duration of hospital stay compared to expectant management or placebo (MD -0.10, 95% CI -0.19 to -0.01) (Analysis 8.8). However, we cannot rule out an important benefit or harm for this outcome for the comparison between suction aspiration versus expectant management or placebo (MD 0.99, 95% CI 0.74 to 1.24) (Analysis 4.9).

Readmission to hospital

The network diagram for the outcome of readmission to hospital is presented in Figure 26. Twelve trial arms contributed towards this outcome. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

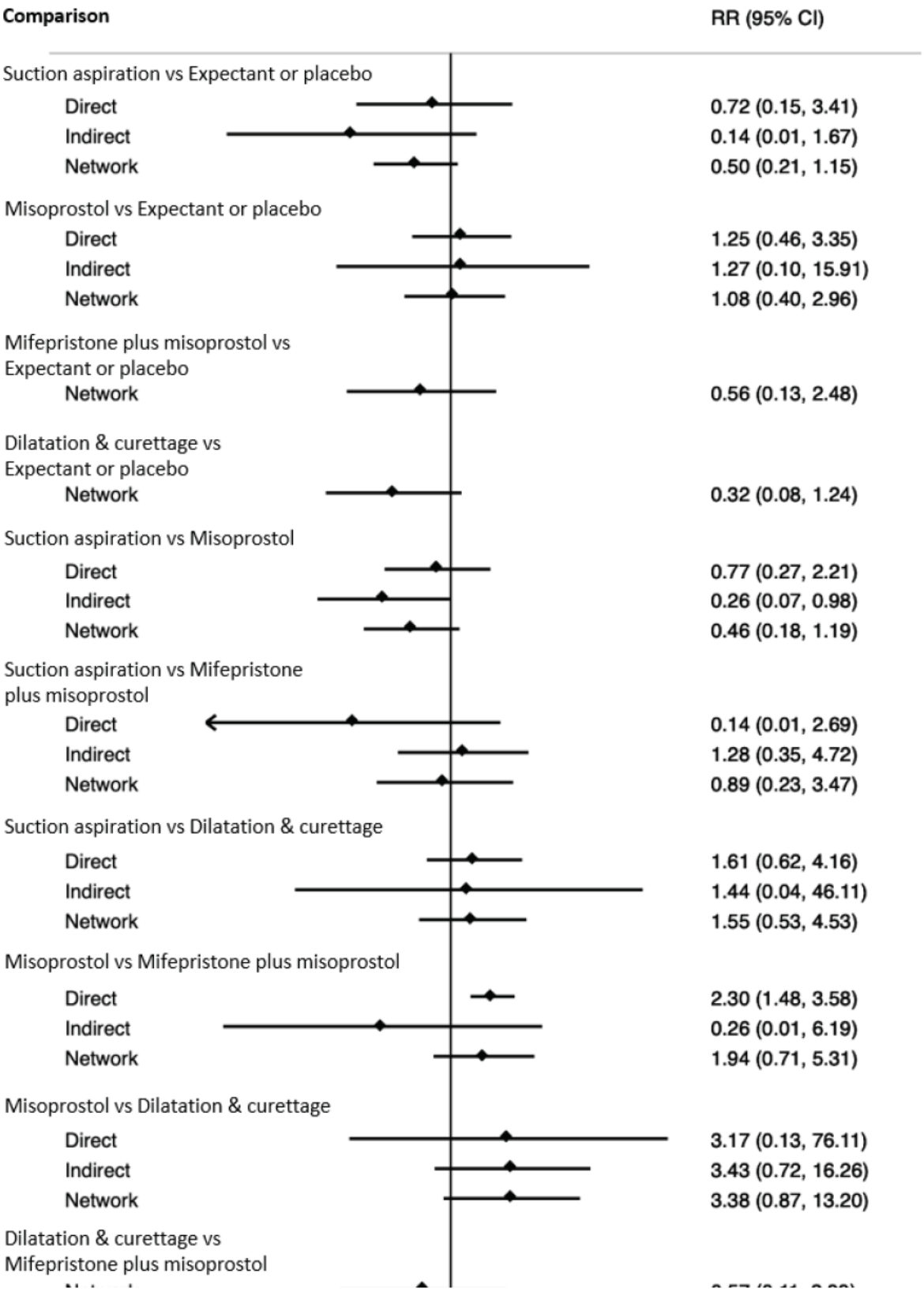
Figure 26. Network diagram for outcome of readmission to hospital. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 10 trials suggest that for suction aspiration (RR 0.50, 95% CI 0.21 to 1.15, *low-certainty evidence*), mifepristone plus misoprostol (RR 0.56, 95% CI 0.13 to 2.48, *low-certainty evidence*), dilatation and curettage (RR 0.32, 95% CI 0.08 to 1.24, *very low-certainty evidence*), and misoprostol (RR 1.08, 95% CI 0.40 to 2.96, *very low-certainty evidence*) were compatible with a wide range of treatment effects for readmission to hospital when compared to expectant management or placebo (Figure 27).

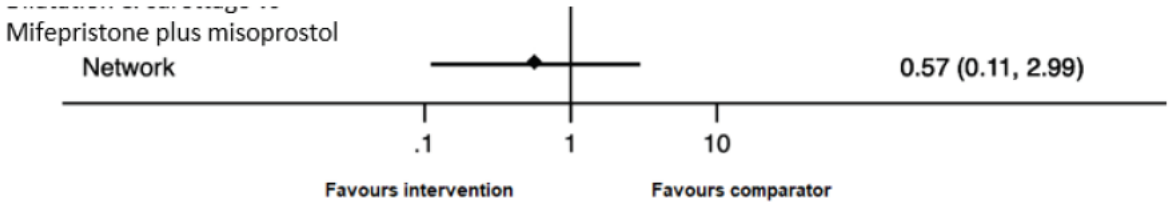
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 27. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for outcome of readmission to hospital.



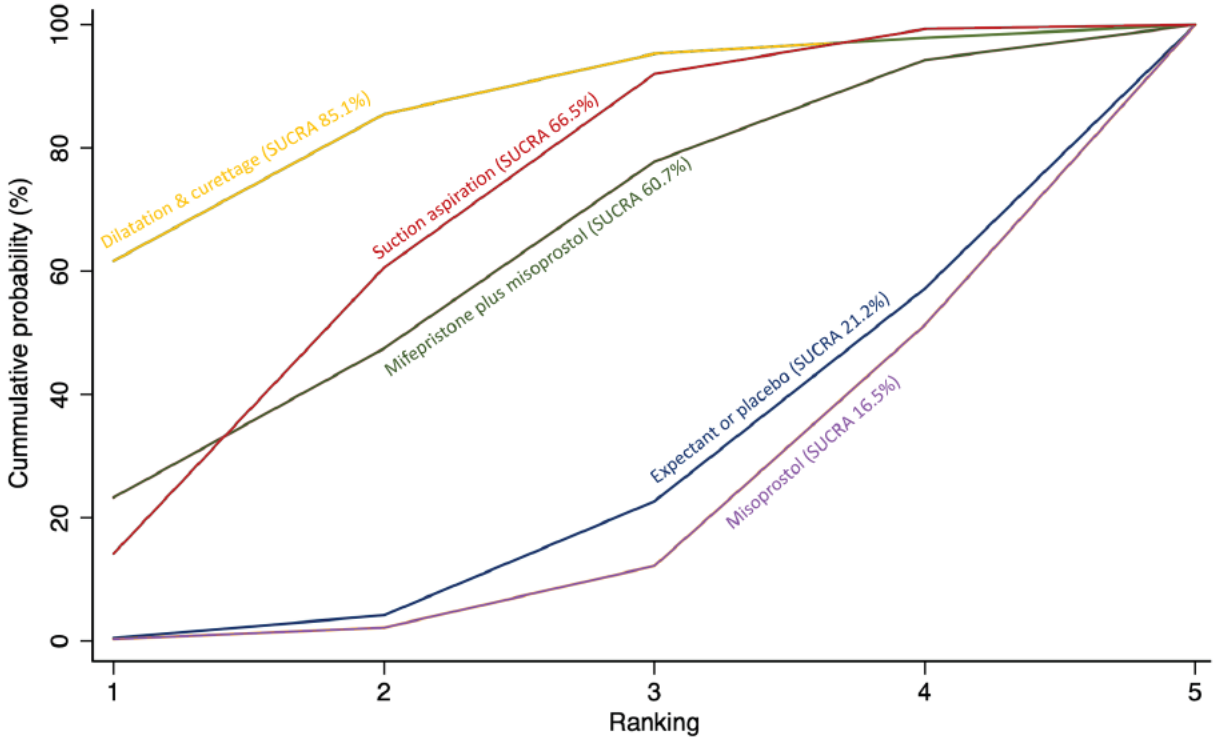
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 27. (Continued)



The cumulative probabilities for each method of managing a miscarriage being at each possible rank for the outcome of readmission to hospital are shown in Figure 28. The highest ranked method for managing a miscarriage for the outcome of readmission to hospital was dilatation and curettage (SUCRA 85.1%), followed by suction aspiration (SUCRA 66.5%), mifepristone plus misoprostol (SUCRA 60.7%) ranked third, expectant management or placebo (SUCRA 21.2%) ranked fourth and misoprostol (SUCRA 16.5%) last.

Figure 28. Cumulative rankogram comparing each of the methods of management of a miscarriage for the outcome of readmission to hospital. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.

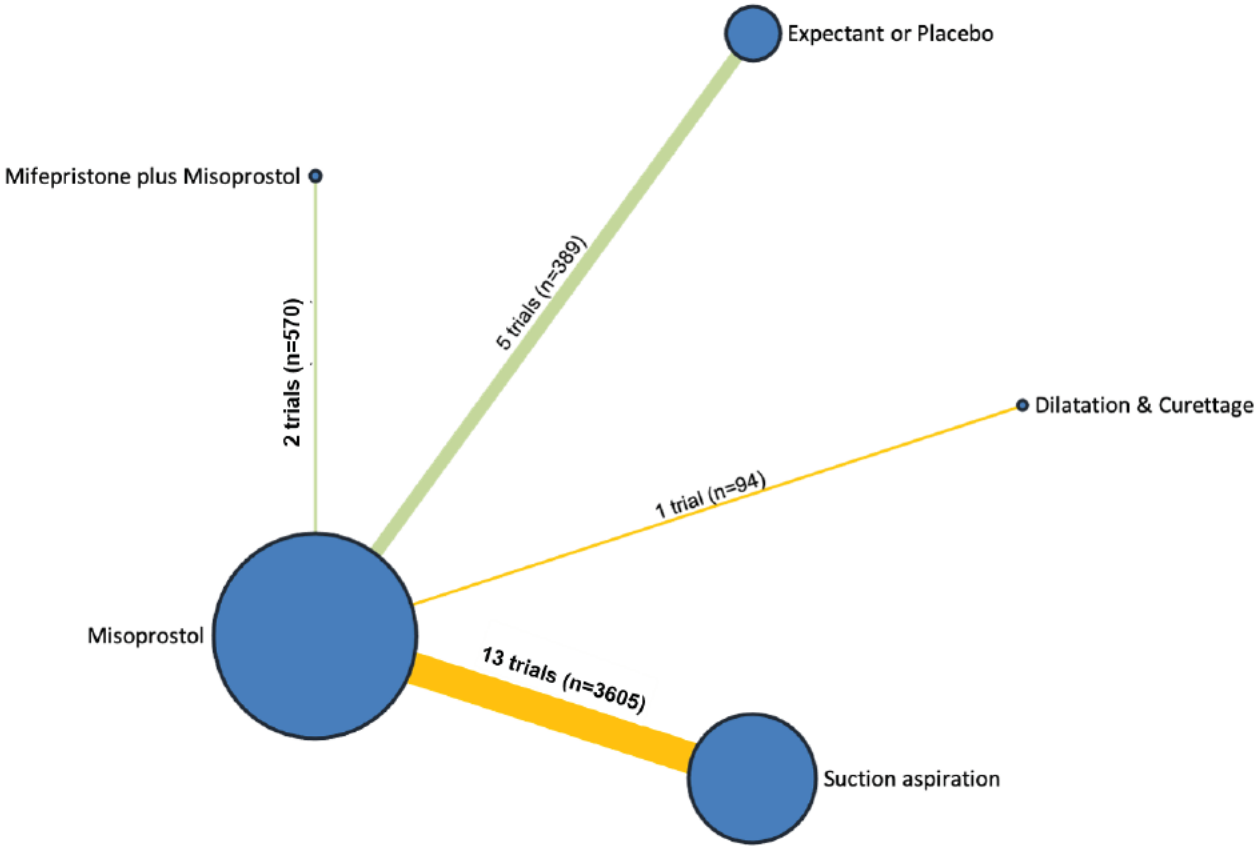


Nausea

The network diagram for the outcome of nausea is presented in Figure 29. Twenty-one trials contributed towards this outcome. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

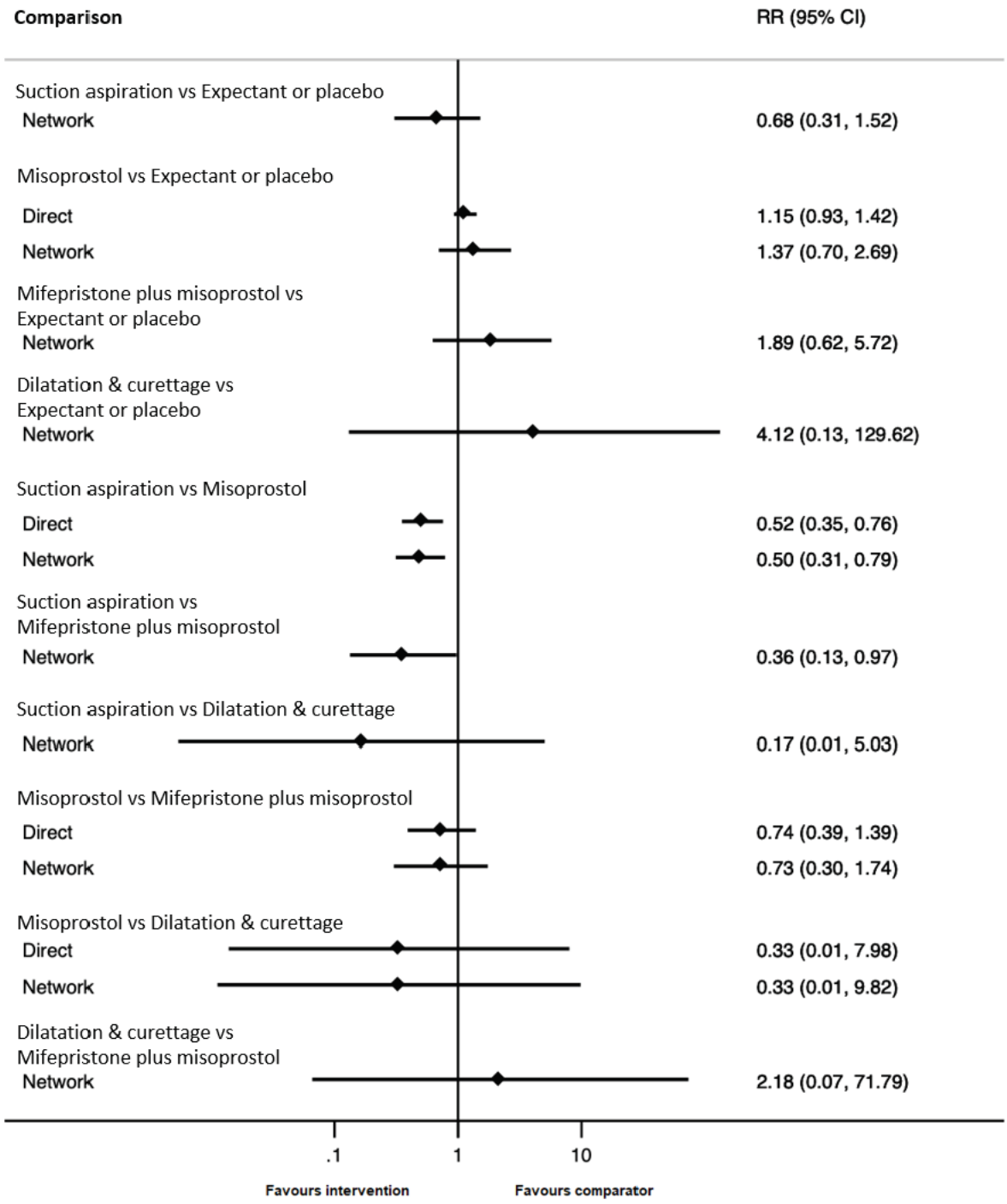
Figure 29. Network diagram for outcome of nausea. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 21 trials suggests that for misoprostol (RR 1.37, 95% CI 0.70 to 2.69, *moderate-certainty evidence*), mifepristone plus misoprostol (RR 1.89, 95% CI 0.62 to 5.72, *moderate-certainty evidence*) and dilatation and curettage (RR 4.12, 95% CI 0.13 to 129.62, *low-certainty evidence*), suction aspiration (RR 0.68, 95% CI 0.31 to 1.52, *very low-certainty evidence*) were compatible with a wide range of treatment effects for nausea when compared to expectant management or placebo (Figure 30).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

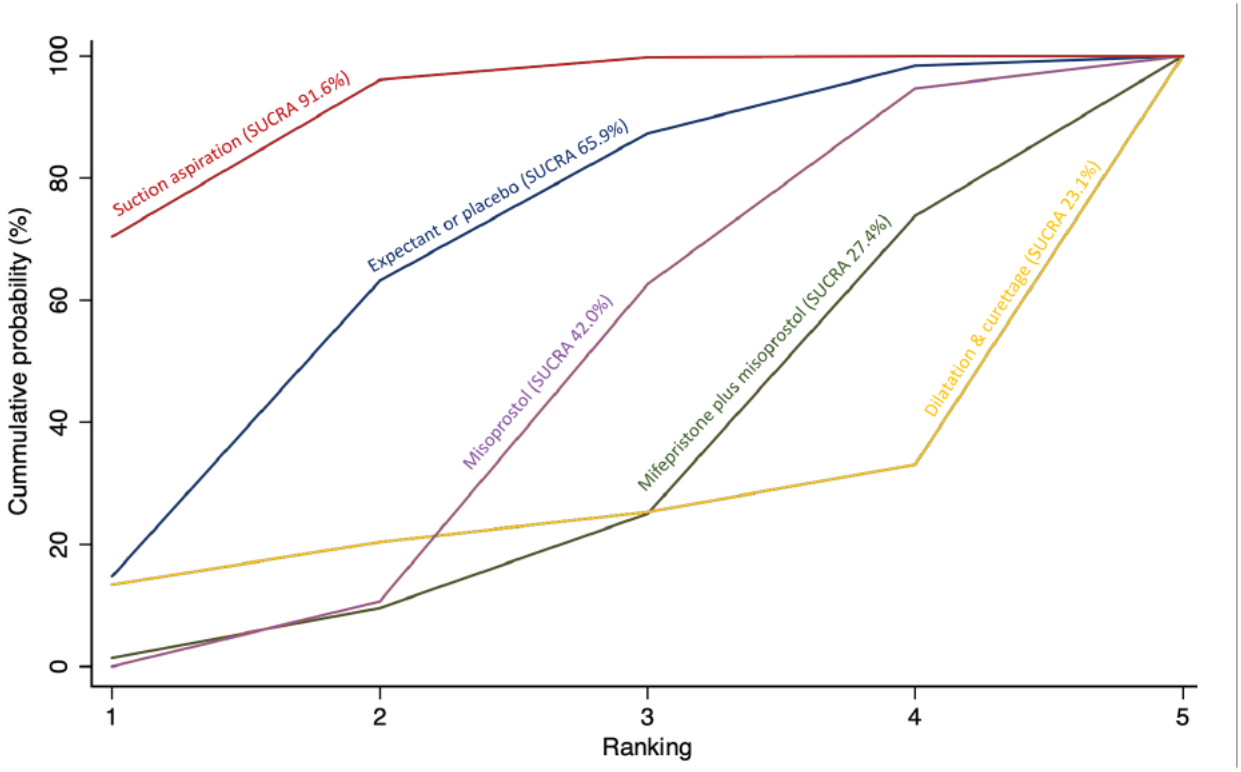
Figure 30. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for outcome of nausea.



The cumulative probabilities for each method of managing a miscarriage being at each possible rank for the outcome of nausea are shown in Figure 31. The highest ranked method for managing a miscarriage for the outcome of nausea was suction aspiration (SUCRA 91.6%), followed by expectant management or placebo (SUCRA 65.9%), misoprostol (SUCRA 42.0%) with mifepristone plus misoprostol (SUCRA 27.4%) ranked fourth and dilatation and curettage (SUCRA 23.1%) last.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 31. Cumulative rankogram comparing each of the methods of management of a miscarriage for the outcome of nausea. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.



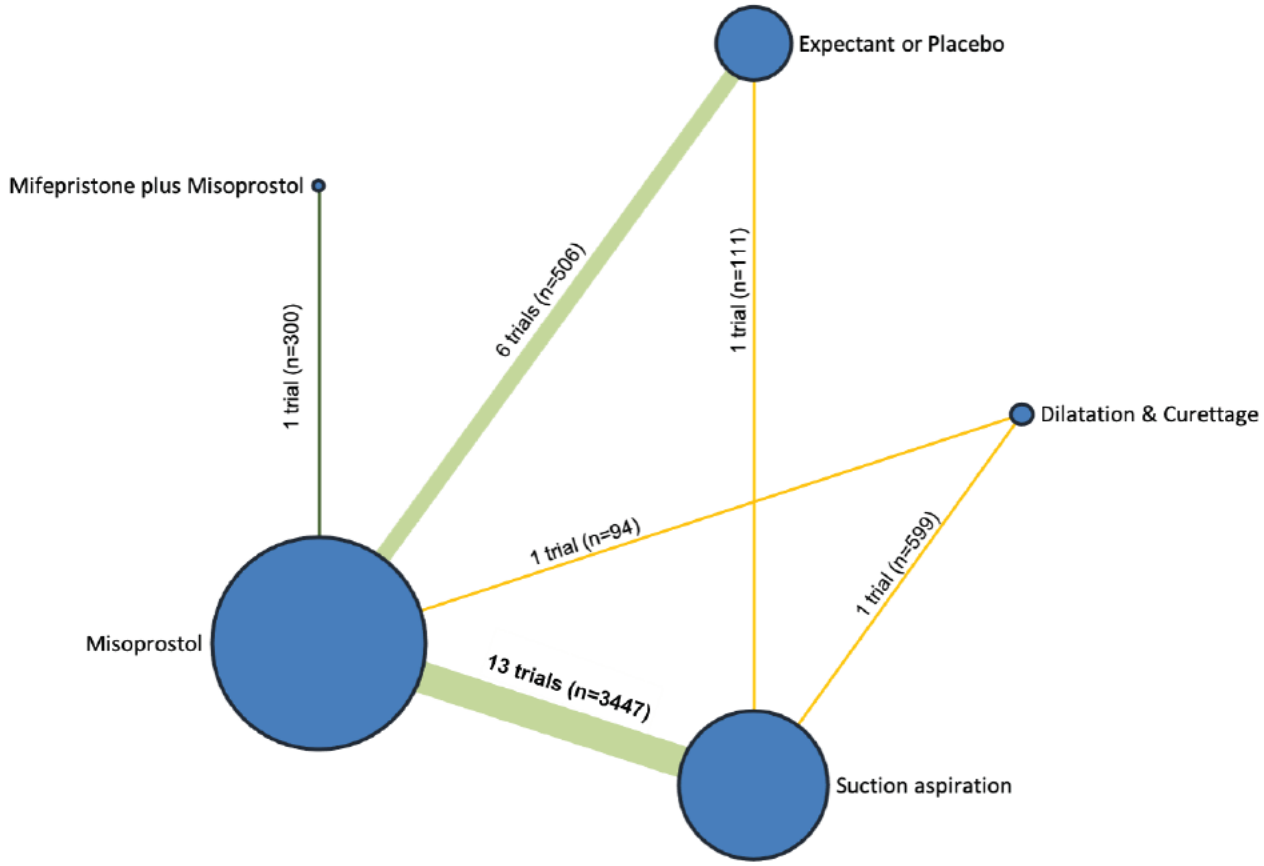
Following assessment using funnel plots, we identified publication bias for the comparison of suction aspiration versus misoprostol for this outcome of nausea. Funnel plots are not included but can be obtained from the author on request.

Vomiting

The network diagram for the outcome of vomiting is presented in Figure 32. 23 trial arms contributed towards this outcome. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

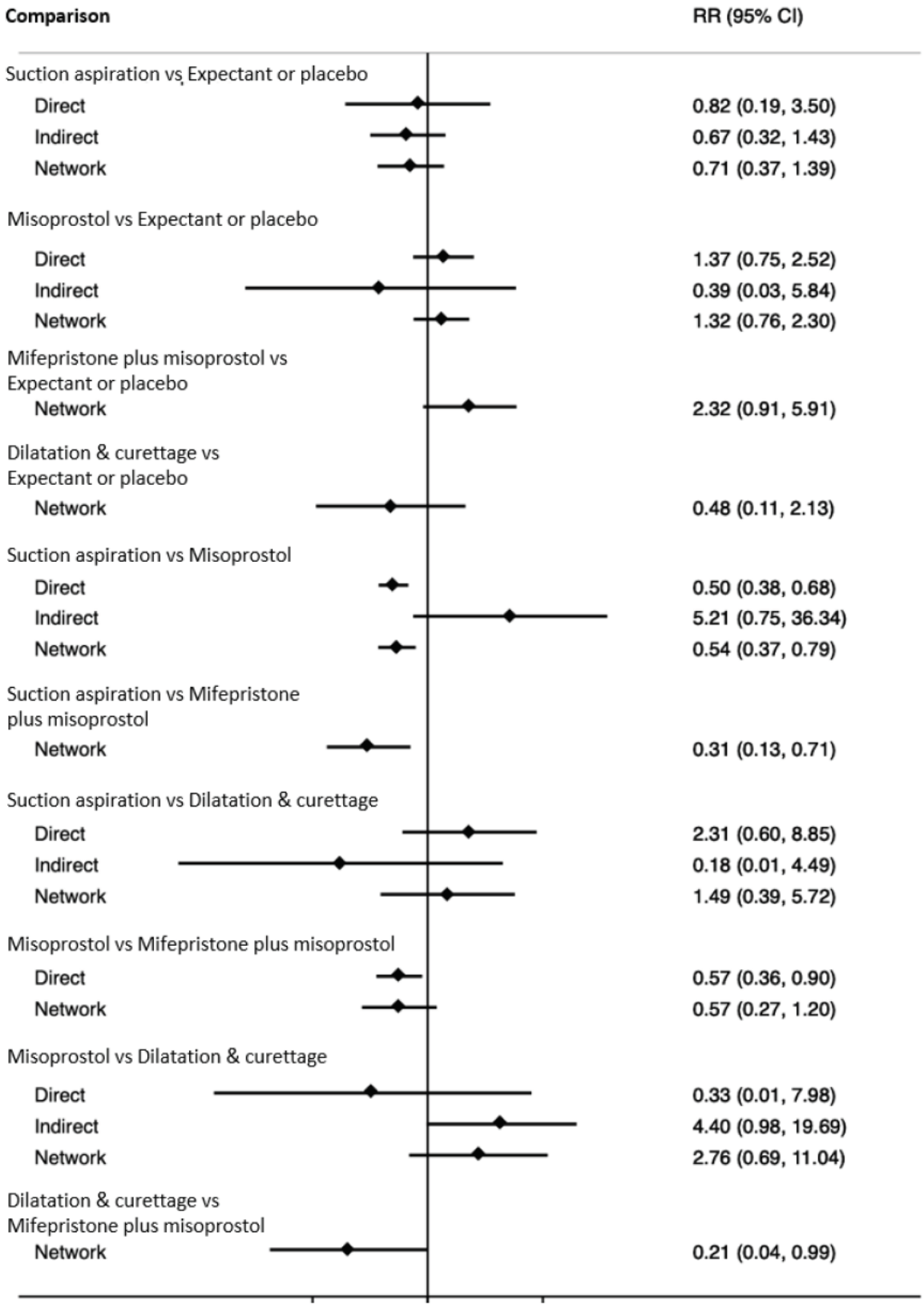
Figure 32. Network diagram for outcome of vomiting. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 21 trials suggest that for suction aspiration (RR 0.71, 95% CI 0.37 to 1.39, *low-certainty evidence*), misoprostol (RR 1.32, 95% CI 0.76 to 2.30, *low-certainty evidence*), dilatation and curettage (RR 0.48, 95% CI 0.11 to 2.13, *low-certainty evidence*) and mifepristone plus misoprostol (RR 2.32, 95% CI 0.91 to 5.91, *low-certainty evidence*) were compatible with a wide range of treatment effects for this outcome when compared with expectant management or placebo (Figure 33).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 33. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for outcome of vomiting.



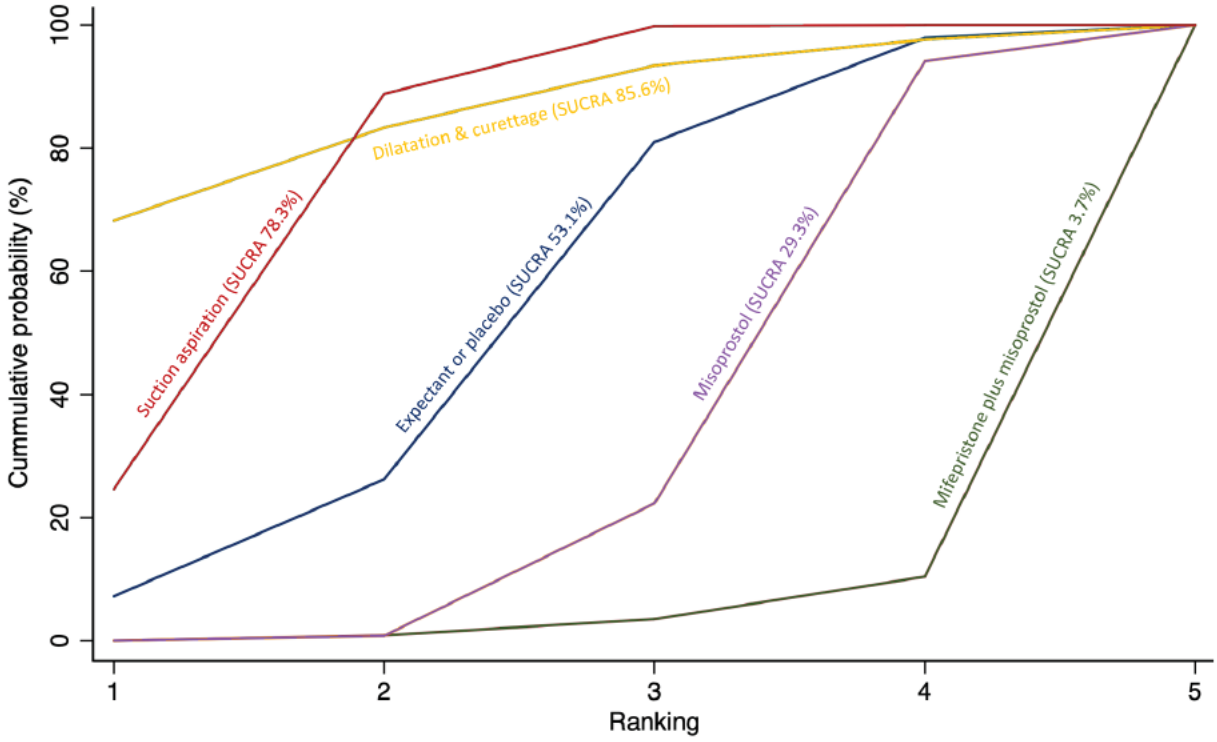
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 33. (Continued)



The cumulative probabilities for each method of managing a miscarriage being at each possible rank for the outcome of vomiting are shown in Figure 34. The highest ranked method for managing a miscarriage for the outcome of vomiting was dilatation and curettage (SUCRA 85.6%), followed by suction aspiration (SUCRA 78.3%), expectant management or placebo (SUCRA 53.1%) with misoprostol (SUCRA 29.3%) ranked fourth and mifepristone plus misoprostol (SUCRA 3.7%) last.

Figure 34. Cumulative rankogram comparing each of the methods of management of a miscarriage for the outcome of vomiting. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.



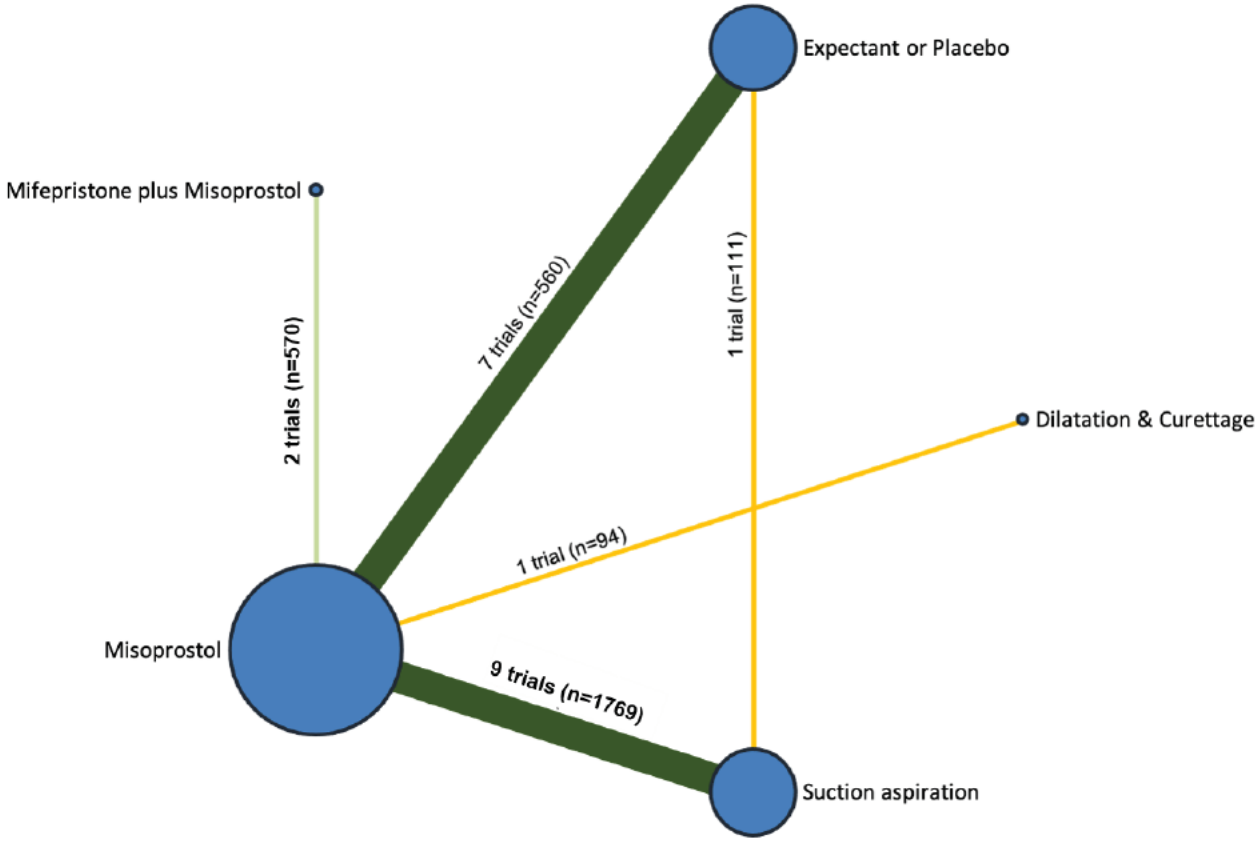
Following assessment using funnel plots, we identified publication bias for the comparison of suction aspiration versus misoprostol for this outcome of vomiting. Funnel plots are not included but can be obtained from the author on request.

Diarrhoea

The network diagram for the outcome of diarrhoea is presented in Figure 35. 20 trial arms contributed towards this outcome. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

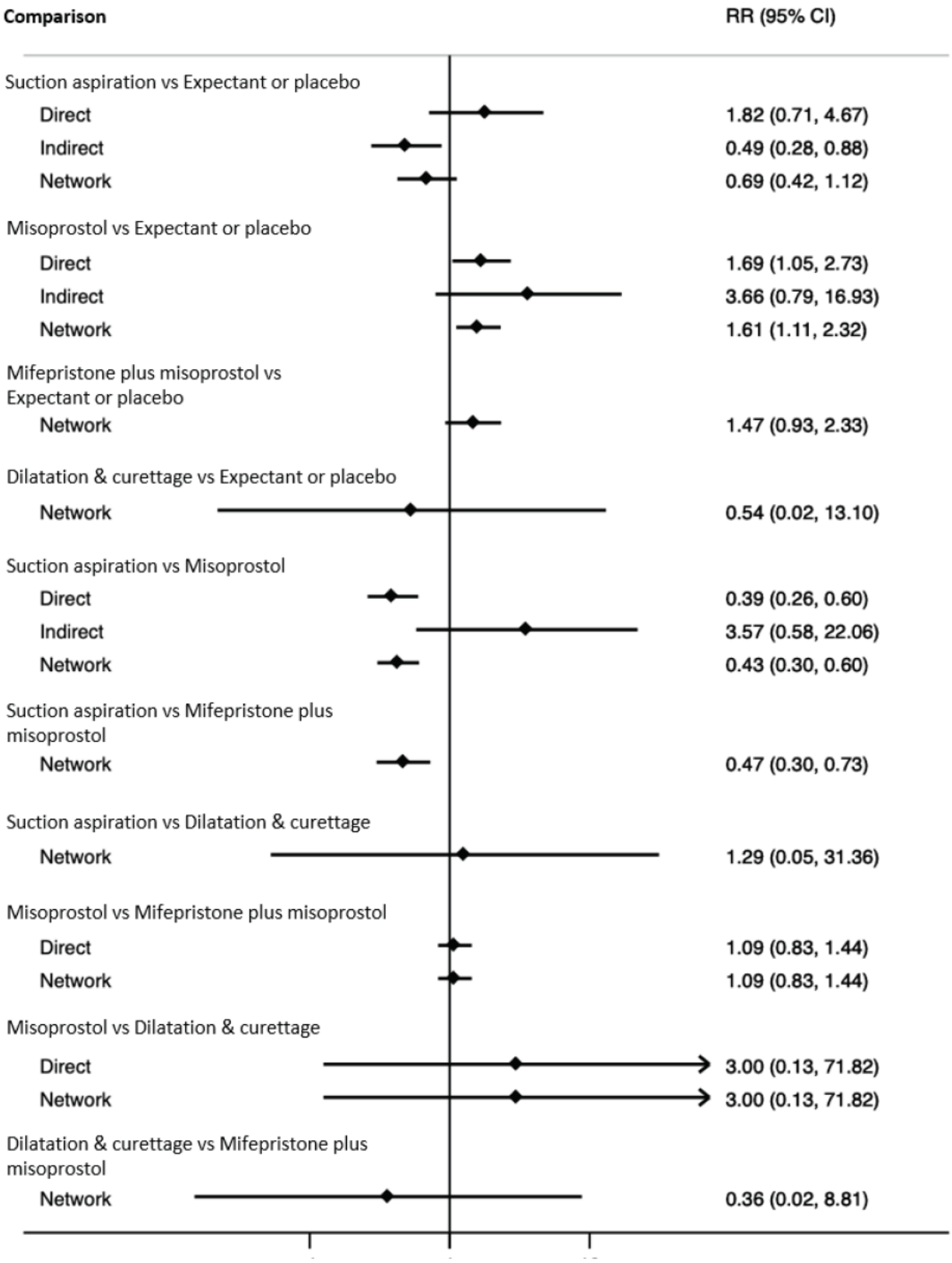
Figure 35. Network diagram for outcome of diarrhoea. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 18 trials, suggest that for suction aspiration (RR 0.69, 95% CI 0.42 to 1.12, *low-certainty evidence*), misoprostol (RR 1.61, 95% CI 1.11 to 2.32, *low-certainty evidence*), mifepristone plus misoprostol (RR 1.47, 95% CI 0.93 to 2.33, *low-certainty evidence*), and dilatation and curettage (RR 0.54, 95% CI 0.02 to 13.10, *very low-certainty evidence*) are compatible with a wide range of treatment effects for diarrhoea when compared with expectant management or placebo (Figure 36).

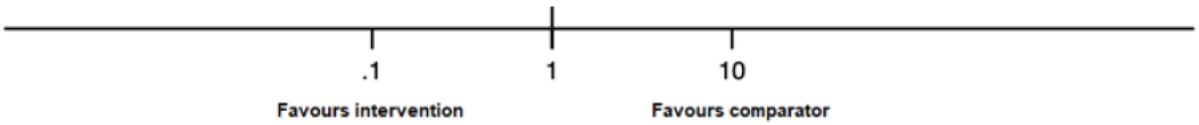
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 36. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for outcome of diarrhoea.



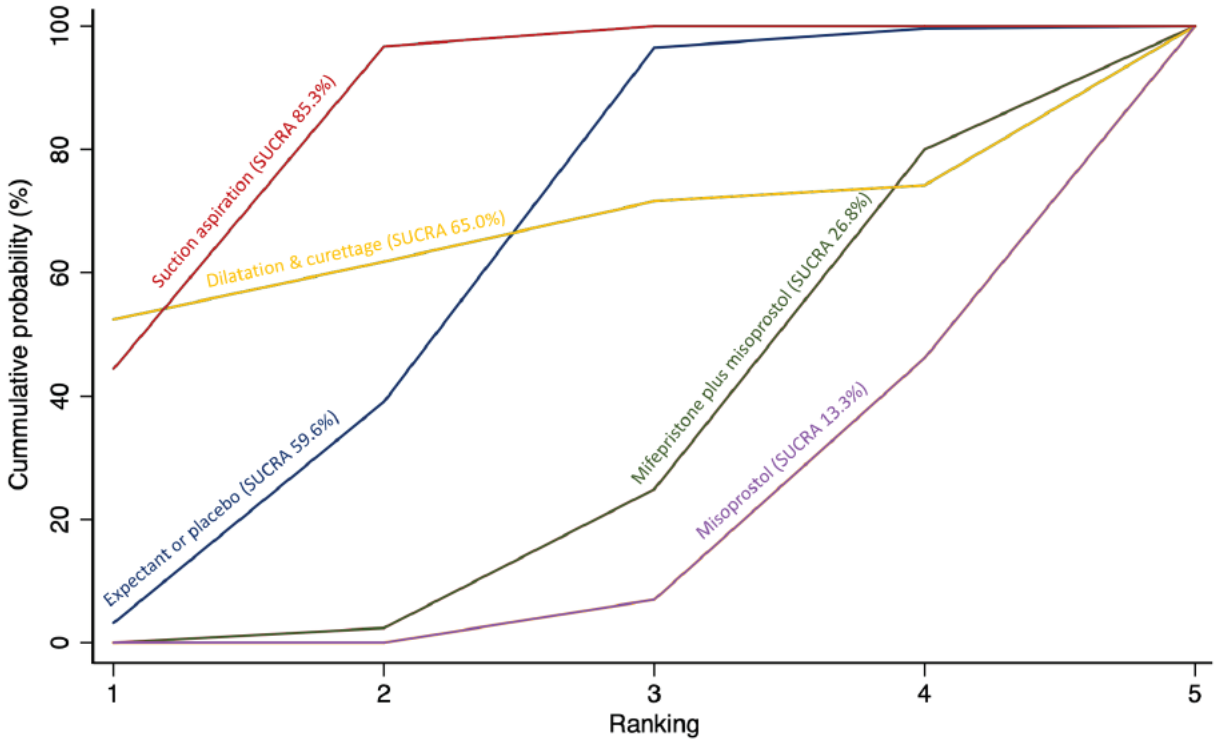
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 36. (Continued)



The cumulative probabilities for each method of managing a miscarriage being at each possible rank for the outcome of diarrhoea are shown in Figure 37. The highest ranked method for managing a miscarriage for the outcome of diarrhoea was suction aspiration (SUCRA 85.3%), followed by dilatation and curettage (SUCRA 65.0%), expectant management or placebo (SUCRA 59.6%) with mifepristone plus misoprostol (SUCRA 26.8%) ranked fourth and misoprostol (SUCRA 13.3%) last.

Figure 37. Cumulative rankogram comparing each of the methods of management of a miscarriage for the outcome of diarrhoea. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.



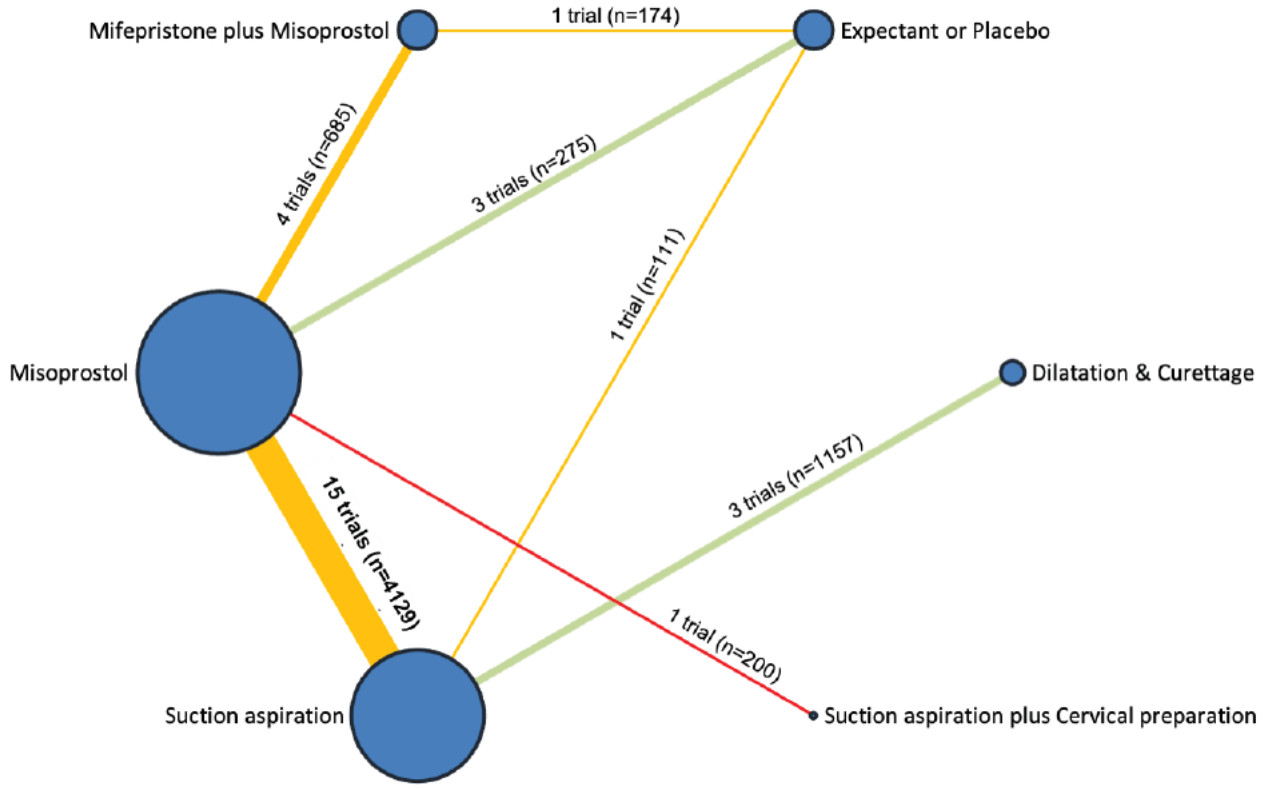
Following assessment using funnel plots, we identified publication bias for the comparison of suction aspiration versus misoprostol for this outcome of diarrhoea. Funnel plots are not included but can be obtained from the author on request.

Pyrexia

The network diagram for the outcome of pyrexia is presented in Figure 38. 28 trial arms contributed towards this outcome. This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

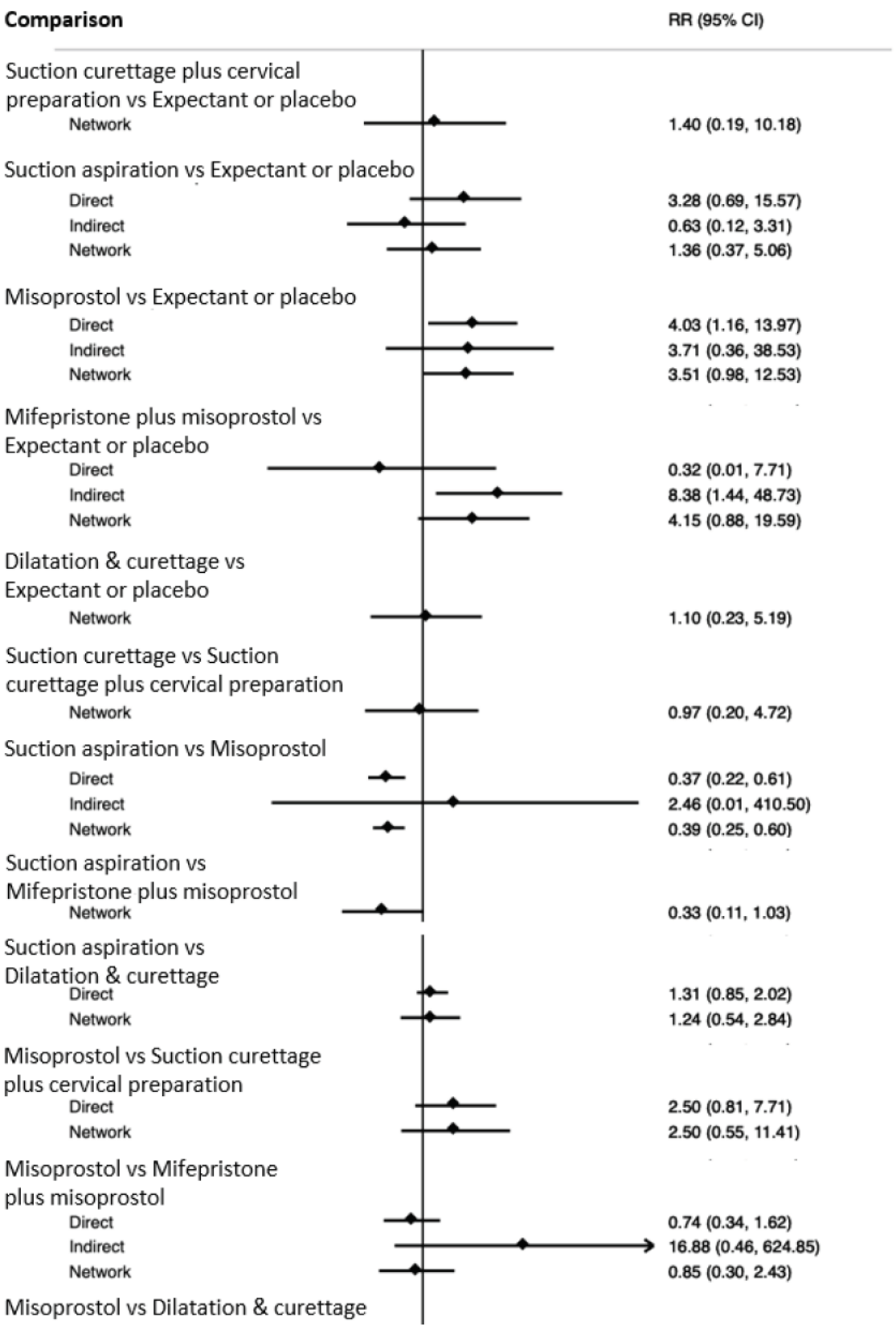
Figure 38. Network diagram for outcome of pyrexia. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 26 trials suggest that for misoprostol (RR 3.51, 95% CI 0.98 to 12.53, *moderate-certainty evidence*) and dilatation and curettage (RR 1.10, 95% CI 0.23 to 5.19, *low-certainty evidence*), suction aspiration (RR 1.36, 95% CI 0.37 to 5.06, *very low-certainty evidence*), suction aspiration plus cervical preparation (RR 1.40, 95% CI 0.19 to 10.18, *very low-certainty evidence*), and mifepristone plus misoprostol (RR 4.15, 95% CI 0.88 to 19.59, *very low-certainty evidence*) were compatible with a wide range of treatment effects for pyrexia when compared with expectant management or placebo (Figure 39).

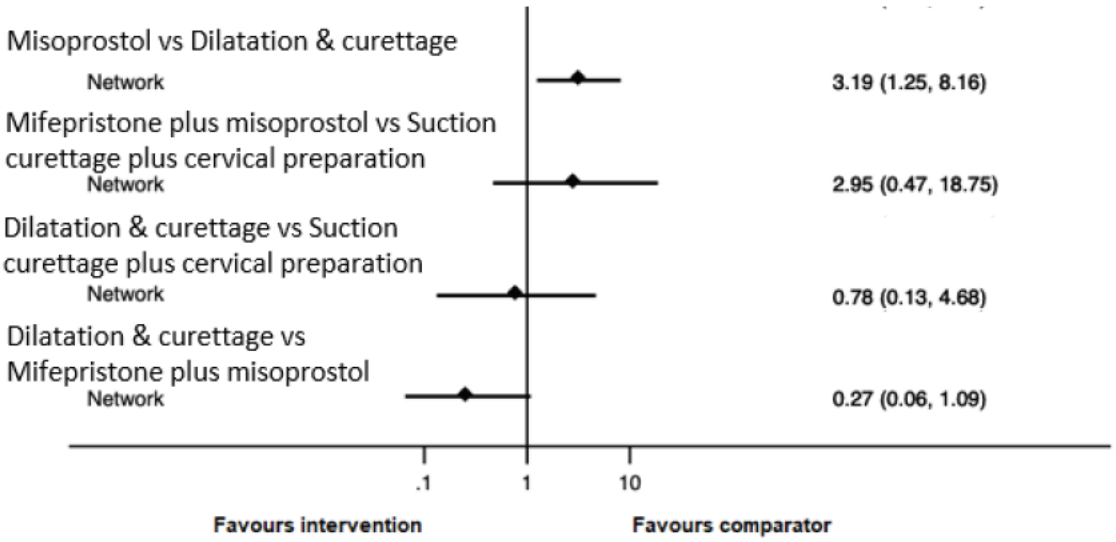
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 39. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for outcome of pyrexia.



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

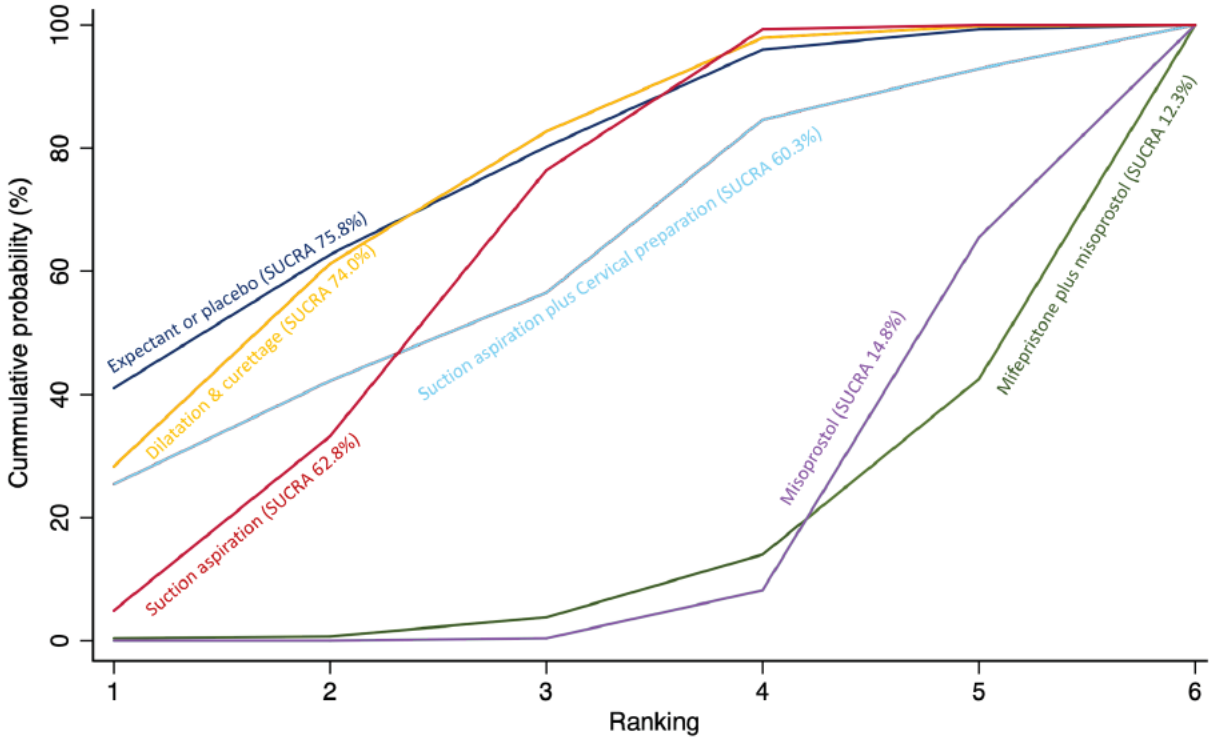
Figure 39. (Continued)



The cumulative probabilities for each method of managing a miscarriage being at each possible rank for the outcome of pyrexia are shown in Figure 40. The highest ranked method for managing a miscarriage for the outcome of pyrexia was expectant management or placebo (SUCRA 75.8%), followed by dilatation and curettage (SUCRA 74.0%), with suction aspiration (SUCRA 62.8%) and suction aspiration plus cervical preparation (SUCRA 60.3%) ranked joint third. Misoprostol (SUCRA 14.8%) ranked fifth with mifepristone plus misoprostol (SUCRA 12.3%) last.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 40. Cumulative rankogram comparing each of the methods of management of a miscarriage for the outcome of pyrexia. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.



Anxiety score

There were two trials which reported anxiety score. Network meta-analysis was therefore not possible, and so we were unable to produce a network diagram, network relative effects and a rankogram. Direct evidence is presented only from pairwise meta-analysis. Both trials (Harwood 2008; Kong 2013) looked at the comparison of suction aspiration versus misoprostol (SMD -0.08, 95% CI -0.24 to 0.09) (Analysis 1.15), with no difference shown.

Depression Score

There were three trials which reported depression score. Network meta-analysis was therefore not possible, so we were unable to produce a network diagram, network relative effects and a rankogram. Direct evidence is presented only from pairwise meta-analysis. Two of the trials were also those that reported anxiety score (Harwood 2008; Kong 2013), and therefore suction aspiration versus misoprostol was the only comparison with more than one trial (SMD -0.17, 95% CI -0.46 to 0.12) (Analysis 1.16), and no difference was shown. The third trial compared misoprostol versus dilatation and curettage.

Subgroup and sensitivity analysis

Statistical inconsistency

We assessed the global statistical inconsistency for the network meta-analyses, which are provided in Appendix 2. A significant inconsistency was observed for the outcomes of complete miscarriage (P = 0.00) and days of bleeding (P = 0.017), and therefore the interpretation of these findings require a high degree of caution. The pairwise meta-analyses also revealed high levels of heterogeneity for the outcome of complete miscarriage which was derived from the type of miscarriage (I^2 range 63% to 94%) (Analysis 1.1; Analysis 1.7; Analysis 2.1; Analysis 3.1; Analysis 3.7; Analysis 4.1; Analysis 4.7; Analysis 5.1; Analysis 5.6; Analysis 6.1; Analysis 6.7; Analysis 8.1; Analysis 8.7; Analysis 9.1; Analysis 9.3; Analysis 10.1). For this reason, a subgroup analysis for missed miscarriage and incomplete miscarriage, which have been identified as the major source of inconsistency and heterogeneity, were conducted for the complete miscarriage outcome.

Type of miscarriage

We carried out subgroup analyses for the primary outcome of complete miscarriage and also days of bleeding by type of miscarriage (incomplete miscarriage versus missed miscarriage).

Missed miscarriage subgroup

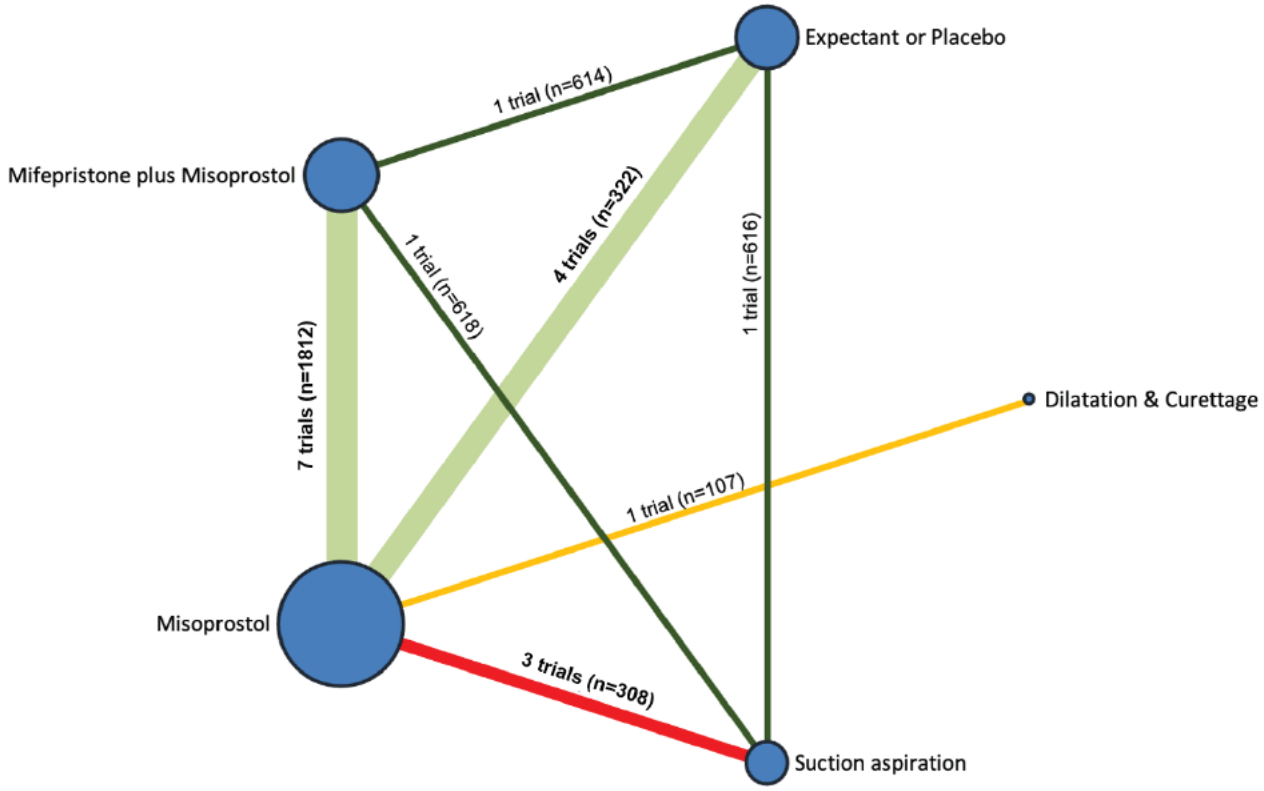
Complete miscarriage

The network diagram for the missed miscarriage subgroup analysis for the outcome of complete miscarriage is presented in Figure 41. Misoprostol was the most frequently investigated method of miscarriage management (12 of 16 trials [75%]) for this subgroup analysis for the outcome of complete miscarriage (Figure 41). This

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

outcome was not reported for any trial involving suction aspiration plus cervical preparation.

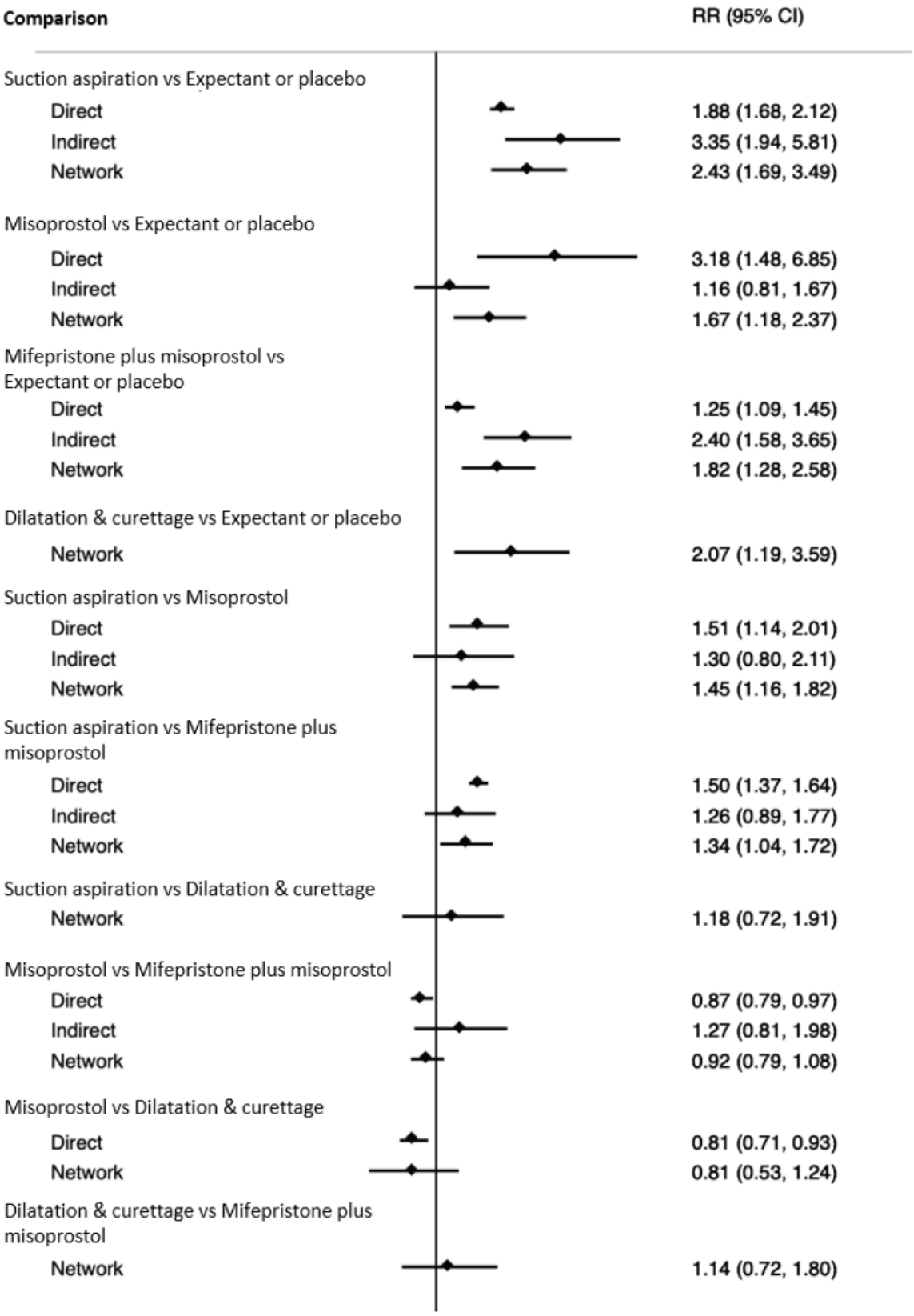
Figure 41. Network diagram for missed miscarriage subgroup analysis of outcome of complete miscarriage. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 16 trials, suggest that dilatation and curettage (RR 2.07, 95% CI 1.19 to 3.59, *high-certainty evidence*) is more effective in achieving a complete miscarriage compared with expectant management or placebo. Misoprostol (RR 1.67, 95% CI 1.18 to 2.37, *low-certainty evidence*), mifepristone plus misoprostol (RR 1.82, 95% CI 1.28 to 2.58, *moderate-certainty evidence*) and suction aspiration (RR 2.43, 95% CI 1.69 to 3.49, *moderate-certainty evidence*) were probably also more effective in achieving a complete miscarriage compared with expectant management or placebo (Figure 42, Summary of findings 2).

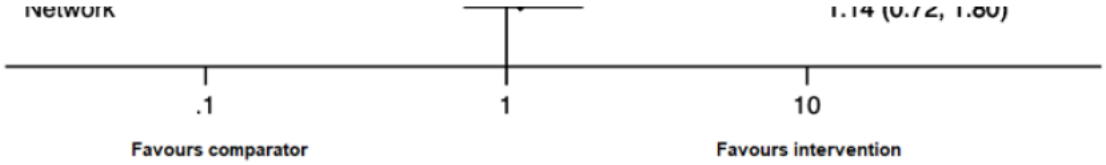
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 42. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for missed miscarriage subgroup of complete miscarriage outcome.



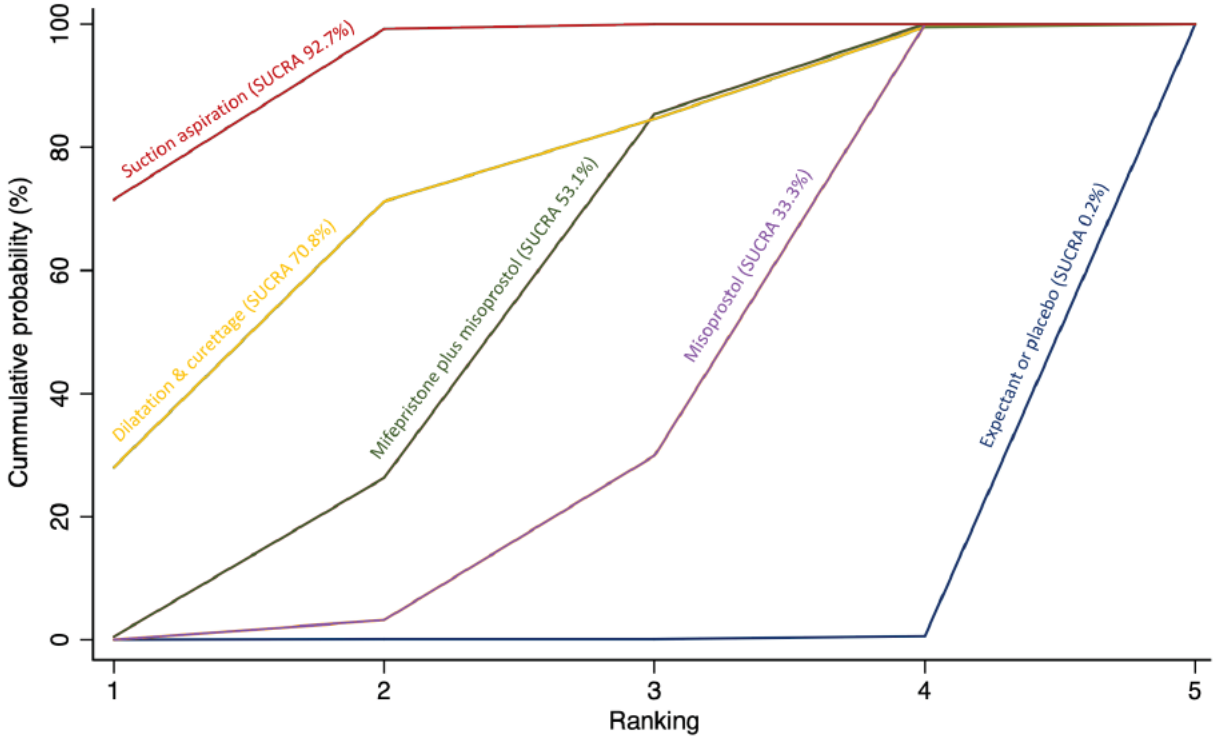
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 42. (Continued)



The cumulative probabilities for each method of managing a miscarriage being at each possible rank for completing a miscarriage are shown in Figure 43. The highest ranked method for managing a miscarriage for the outcome of complete miscarriage in the missed miscarriage subgroup was suction curettage (SUCRA 92.7%), followed by dilatation and curettage (SUCRA 70.8%), mifepristone plus misoprostol (SUCRA 53.1%) with misoprostol (SUCRA 33.3%) ranked fourth and expectant management or placebo (SUCRA 0.2%) last.

Figure 43. Cumulative rankogram comparing each of the methods of management of a miscarriage for missed miscarriage subgroup analysis for the outcome of complete miscarriage. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.

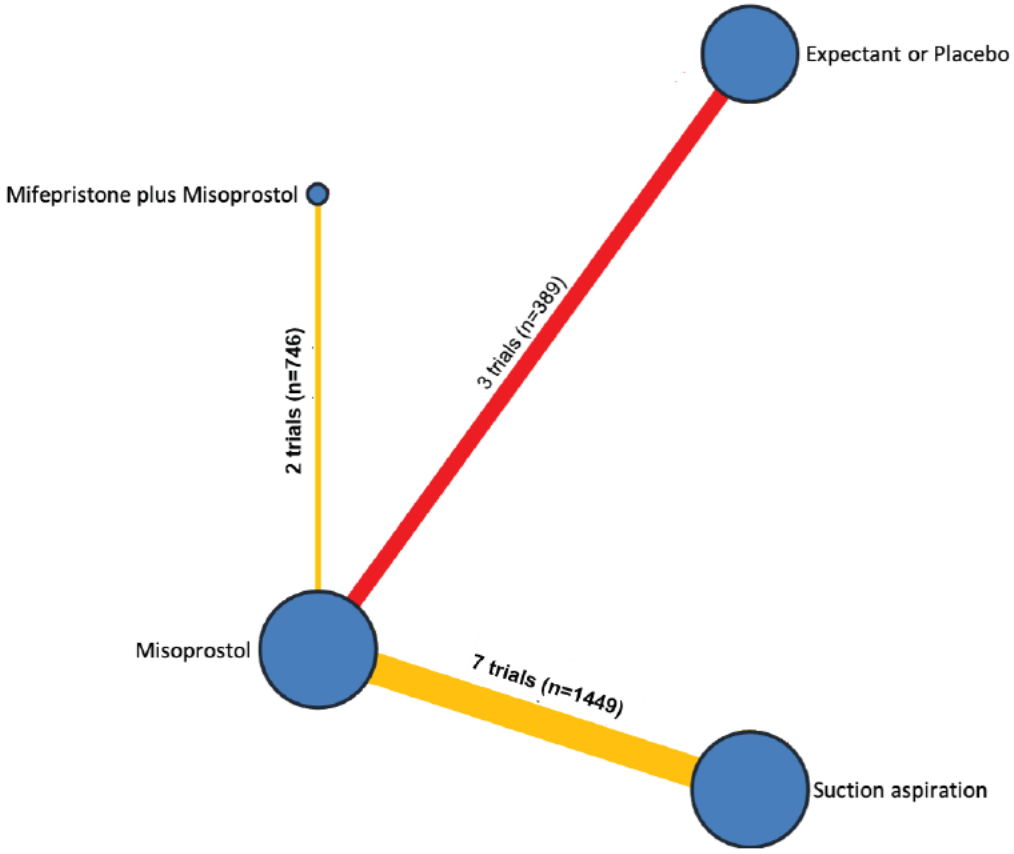


Days of bleeding

The network diagram for the missed miscarriage subgroup analysis for the outcome of days of bleeding is presented in Figure 44.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

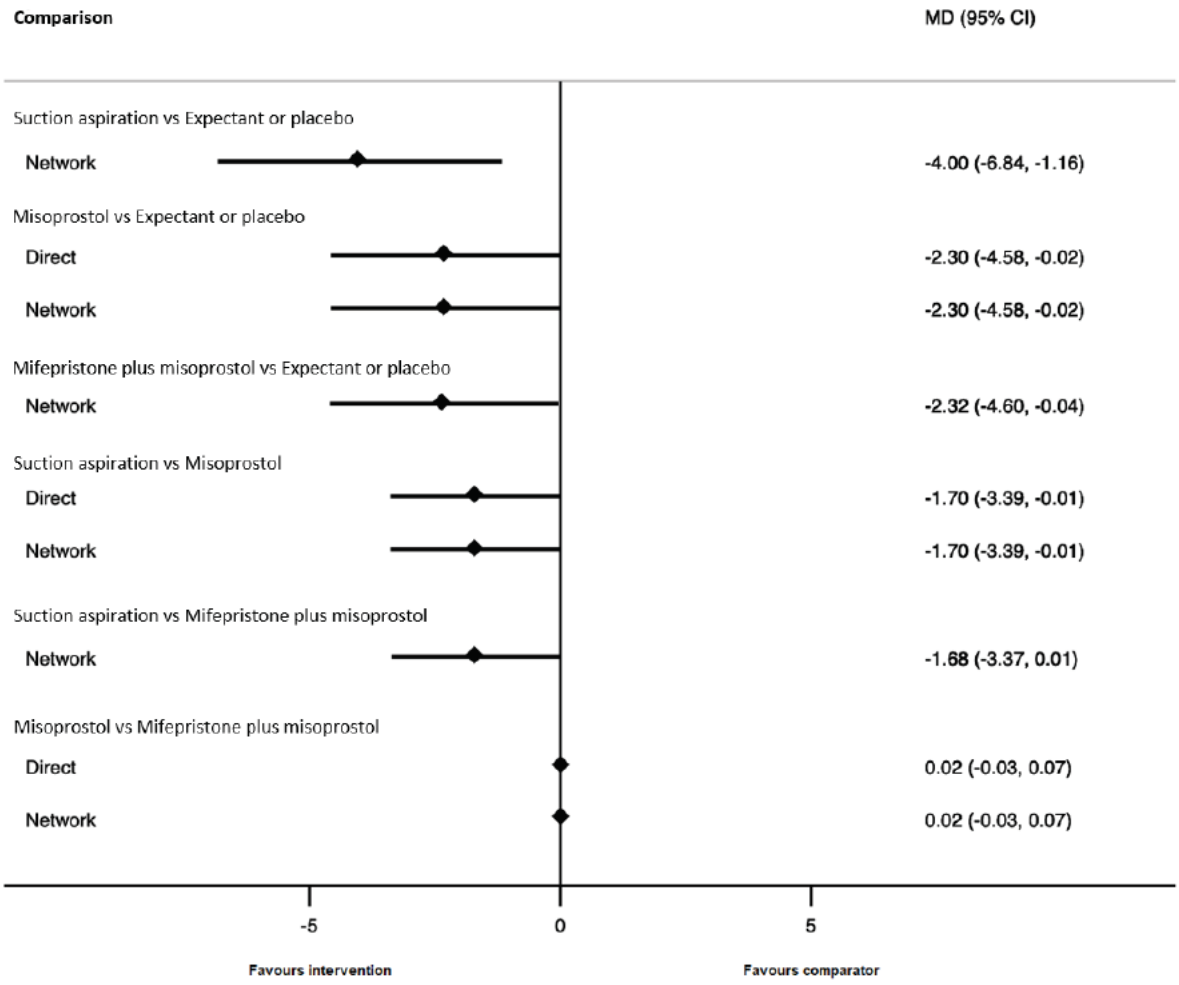
Figure 44. Network diagram for missed miscarriage subgroup analysis of outcome of days of bleeding. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 12 trials, suggest that suction aspiration (RR -4.00, 95% CI -6.84 to -1.16, *very low-certainty evidence*), mifepristone plus misoprostol (RR -2.32, 95% CI -4.60 to -0.04, *very* low-*certainty evidence*) and misoprostol (RR -2.30, 95% CI -4.58 to -0.02, *very low-certainty evidence*) may cause less days of bleeding when compared to expectant management or placebo, but the evidence is very uncertain (Figure 45).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

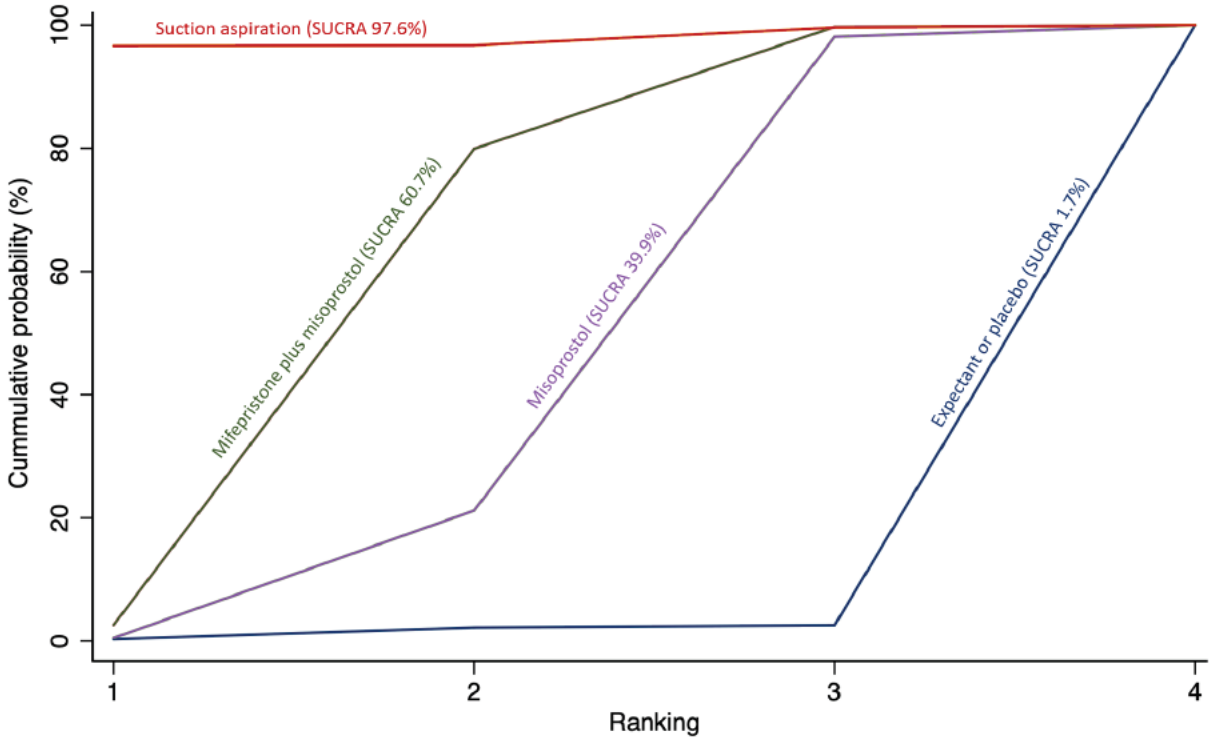
Figure 45. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for missed miscarriage subgroup of the days of bleeding outcome.



The cumulative probabilities for each method of managing a miscarriage being at each possible rank for the outcome of days of bleeding are shown in Figure 46. The highest ranked method for managing a miscarriage for the outcome of days of bleeding was suction aspiration (SUCRA 97.6%), followed by mifepristone plus misoprostol (SUCRA 60.7%), misoprostol (SUCRA 39.9%) with expectant management or placebo (SUCRA 1.7%) last.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 46. Cumulative rankogram comparing each of the methods of management of a miscarriage for missed miscarriage subgroup analysis for the outcome of days of bleeding. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.



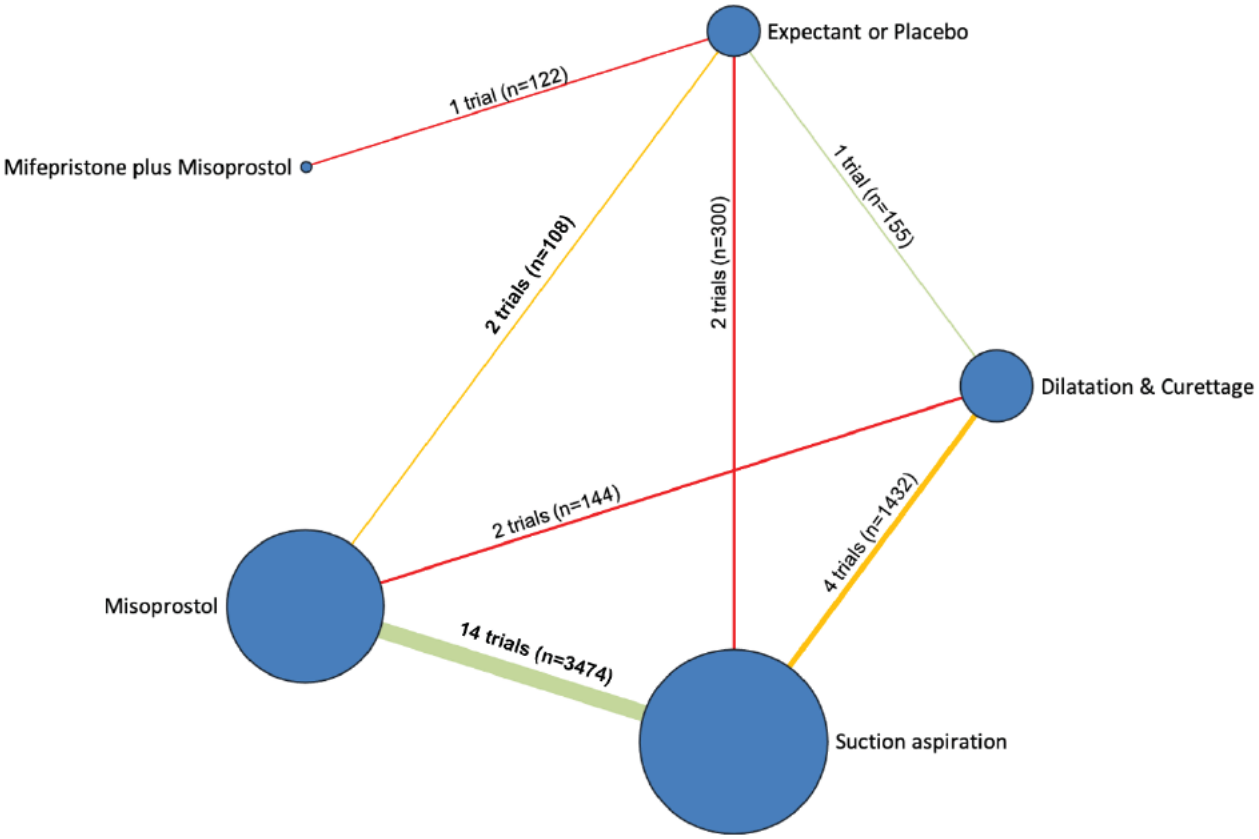
Incomplete miscarriage subgroup

Compete miscarriage

The network diagram for the incomplete miscarriage subgroup analysis for the outcome of complete miscarriage is presented in Figure 47. Suction curettage was the most frequently investigated method of miscarriage management (18 of 26 trials [69%]) for this subgroup analysis for the outcome of complete miscarriage (Figure 47). This outcome was not reported for any trial involving suction aspiration plus cervical preparation.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

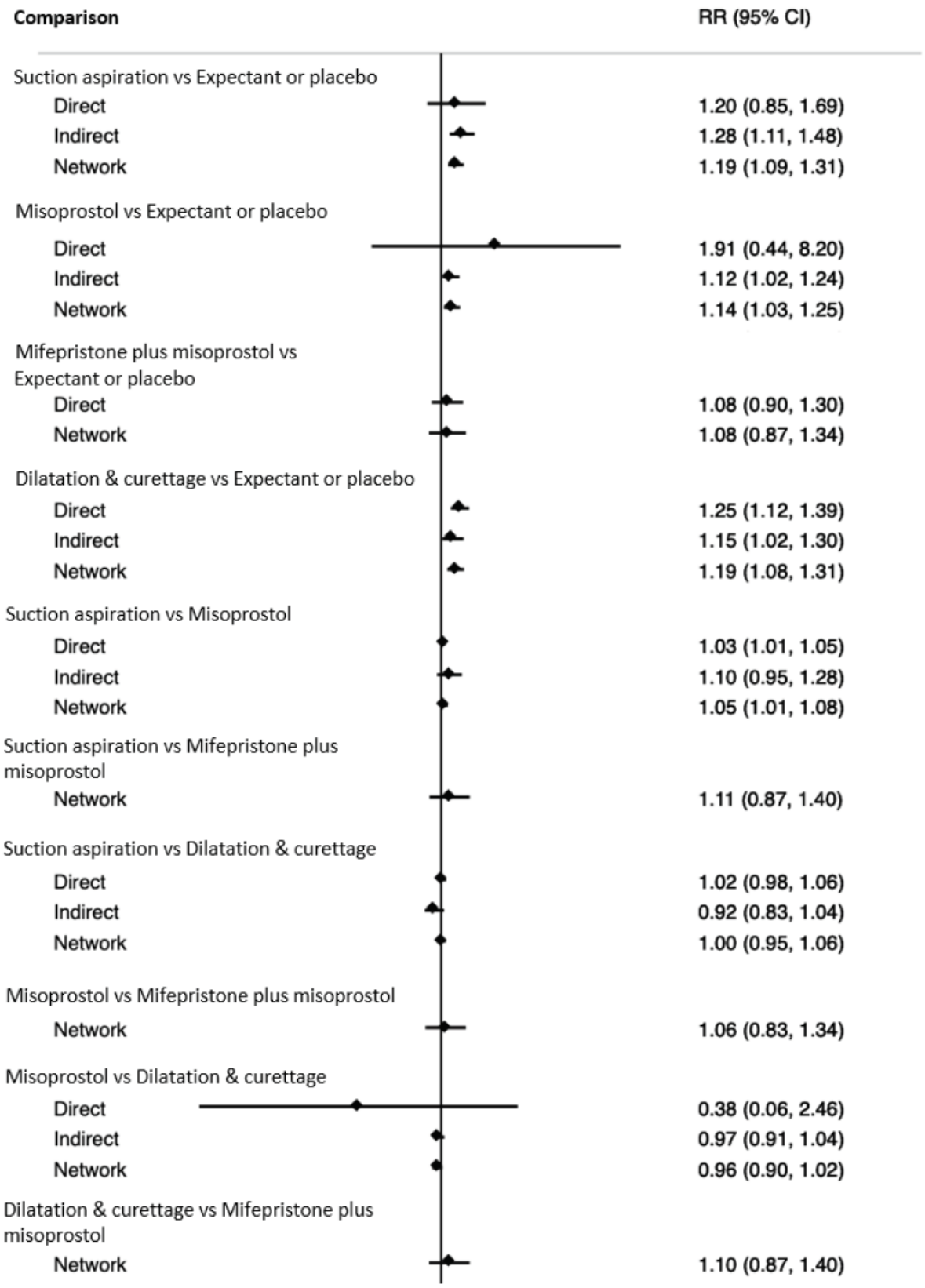
Figure 47. Network diagram for incomplete miscarriage subgroup analysis of outcome of complete miscarriage. The nodes represent an intervention and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



Relative effects from the network meta-analysis of 26 trials suggest that misoprostol (RR 1.14, 95% CI 1.03 to 1.25, *moderate-certainty evidence*), dilatation and curettage (RR 1.19, 95% CI 1.08 to 1.31, *moderate-certainty evidence*) and suction aspiration (RR 1.19, 95% CI 1.09 to 1.31, *moderate-certainty evidence*) were probably more effective in achieving a complete miscarriage compared with expectant management or placebo. Mifepristone plus misoprostol (RR 1.08, 95% CI 0.87 to 1.34, *very low-certainty evidence*) was compatible with a wide range of treatment effects for the outcome of complete miscarriage compared with expectant management or placebo (Figure 48, Summary of findings 3).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 48. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for incomplete miscarriage subgroup of complete miscarriage outcome.



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 48. (Continued)

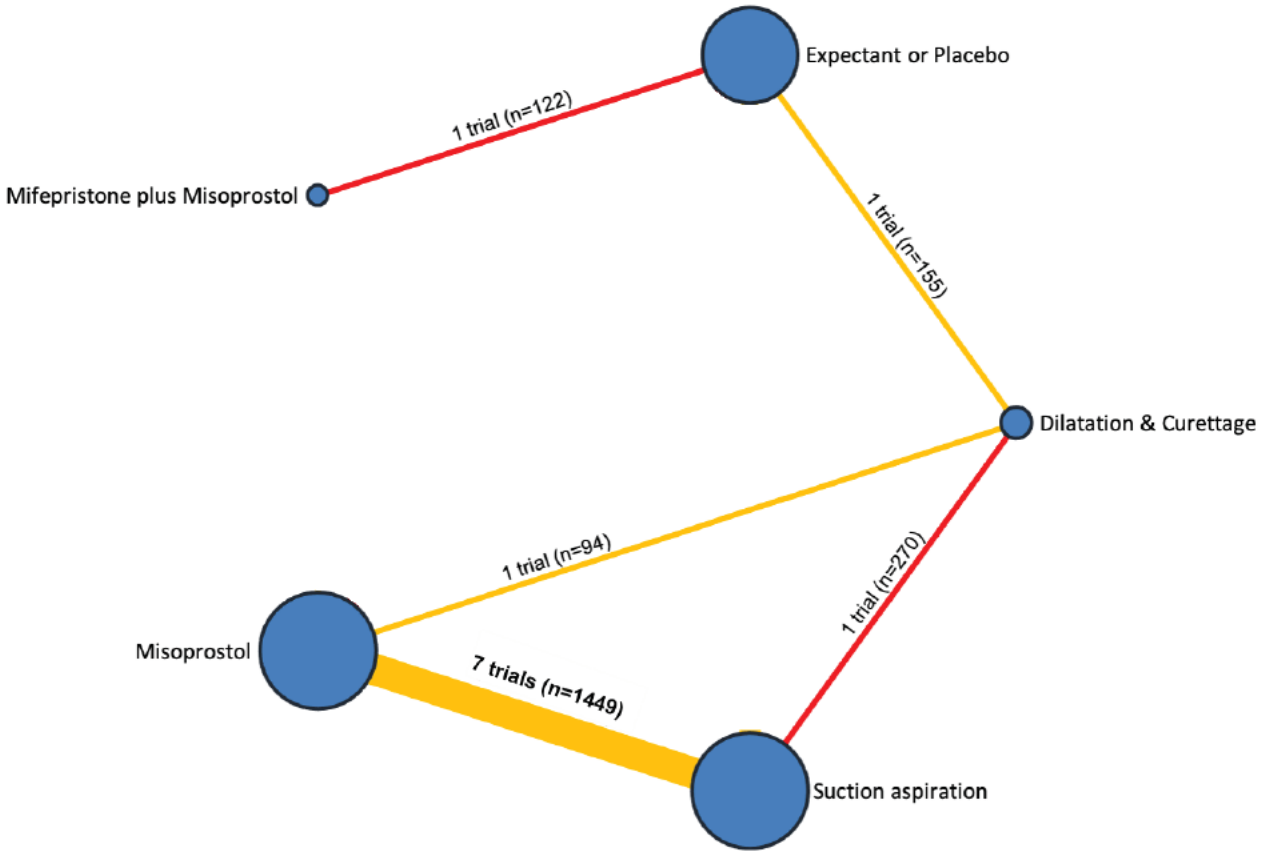


The cumulative probabilities for each method of managing a miscarriage being at each possible rank for completing a miscarriage are shown in Figure 5. The highest ranked method for managing a miscarriage for the outcome of complete miscarriage in the incomplete miscarriage subgroup was suction aspiration (SUCRA 83.6%), followed by dilatation and curettage (SUCRA 79.4%), misoprostol (SUCRA 44.2%) with mifepristone plus misoprostol ranked fourth (SUCRA 36.1%) and expectant management or placebo (SUCRA 6.7%) last.

Days of bleeding

The network diagram for the missed miscarriage subgroup analysis for the outcome of days of bleeding is presented in Figure 49.

Figure 49. Network diagram for incomplete miscarriage subgroup analysis of outcome of days of bleeding. 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 and are drawn proportional to the number of trials making each direct comparison. Numbers on the lines represent the number of trials and participants for each comparison. The colour of the line is green for high-certainty evidence; light green for moderate-certainty evidence; orange for low-certainty evidence and red for very low-certainty evidence. Multi-arm trials contribute to more than one comparison.



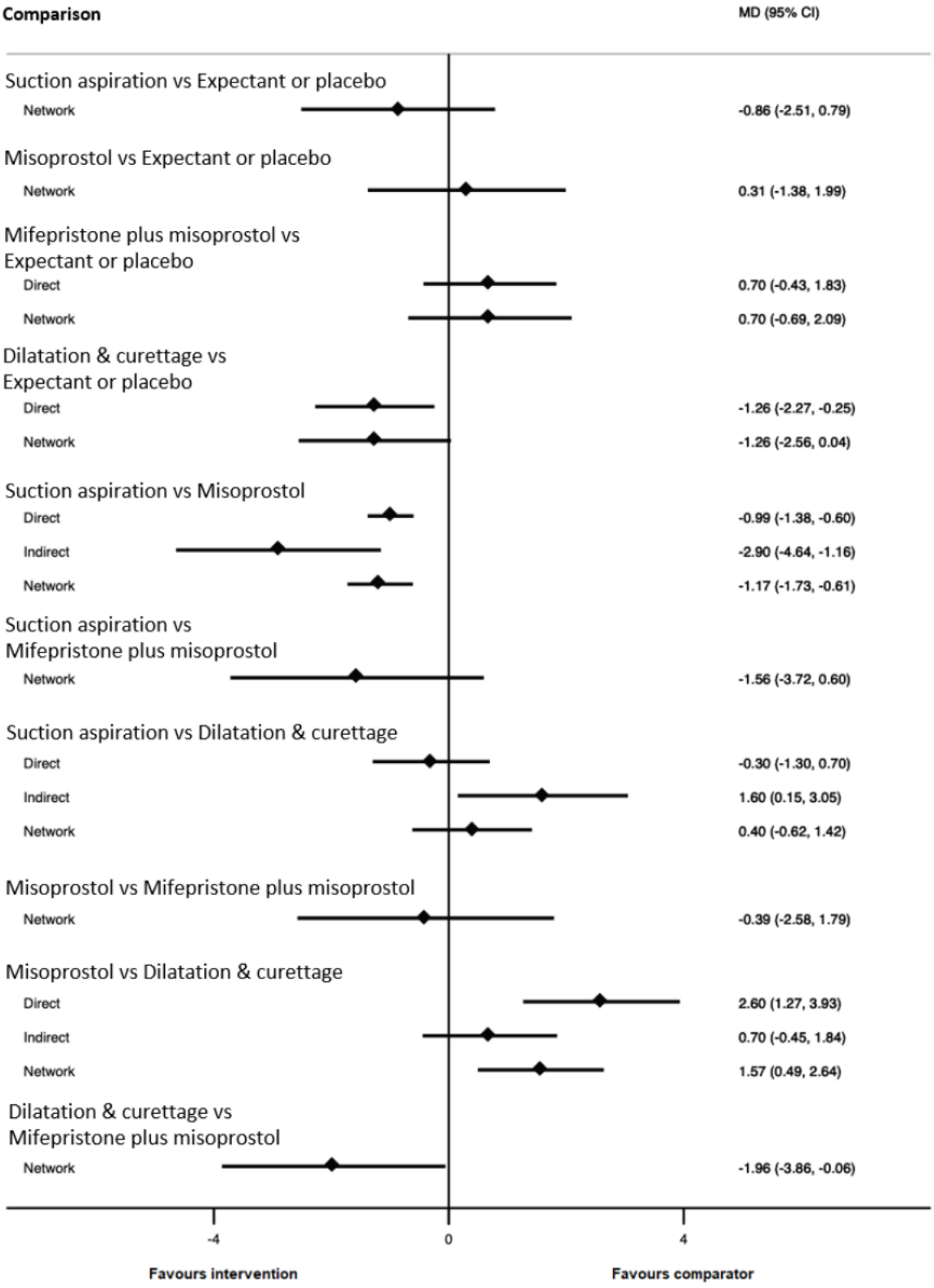
Relative effects from the network meta-analysis of 11 trials, suggest that suction aspiration (RR -0.86, 95% CI -2.51 to 0.79, very *low-certainty evidence*), mifepristone plus misoprostol (RR 0.70, 95% CI -0.69 to 2.09, *very* low-*certainty evidence*), misoprostol (RR 0.31,

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

95% CI -1.38 to 1.99, *very* low-*certainty evidence*) and dilatation and curettage (RR -1.26, 95% CI -2.56 to 0.04, *very* low-*certainty evidence*) were compatible with a wide range of treatment effects for days of bleeding when compared with expectant management or placebo, and the evidence is very uncertain (Figure 50).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 50. Forest plot with relative risk ratios and 95% CIs from pairwise, indirect and network (combining direct and indirect) analyses for incomplete miscarriage subgroup of the days of bleeding outcome.

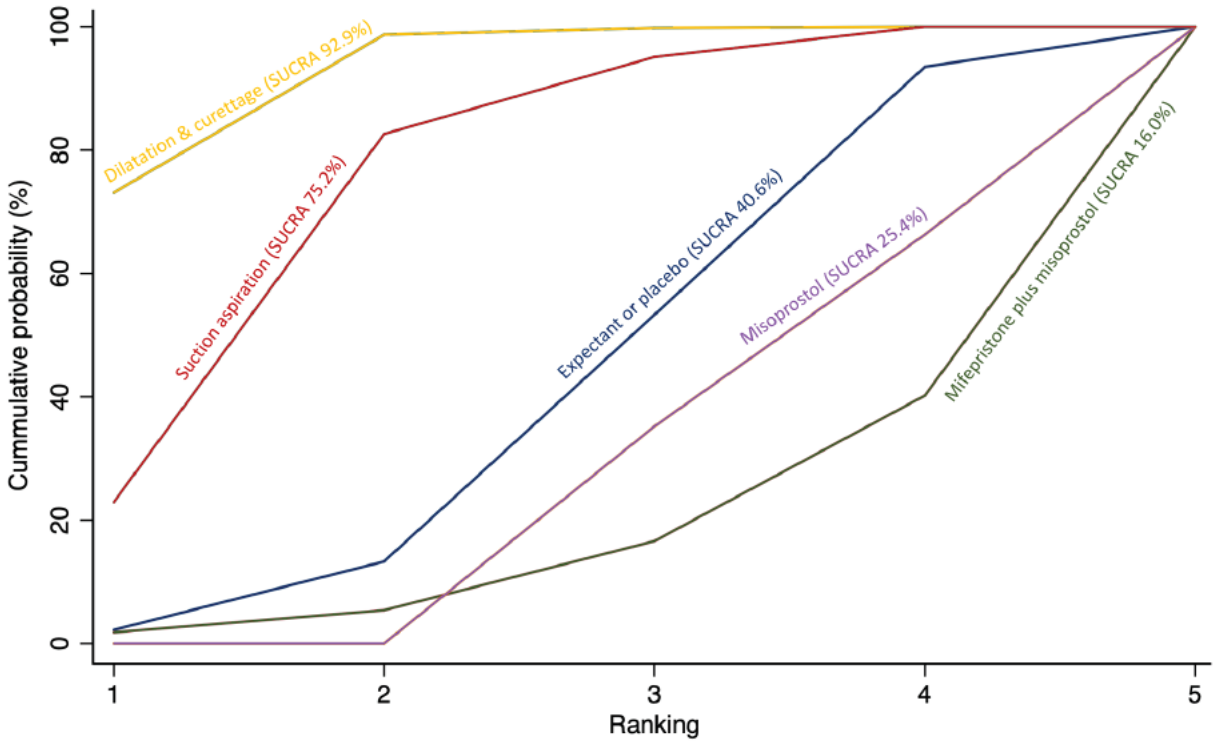


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 50. (Continued)

The cumulative probabilities for each method of managing a miscarriage being at each possible rank for the outcome of days of bleeding are shown in Figure 51. The highest ranked method for managing a miscarriage for the outcome of days of bleeding in the missed miscarriage subgroup was dilatation and curettage (SUCRA 92.9%), followed by suction aspiration (SUCRA 75.2%), followed by expectant or placebo (SUCRA 40.6%), misoprostol (SUCRA 25.4%) ranked fourth and mifepristone plus misoprostol (SUCRA 16.0%) last.

Figure 51. Cumulative rankogram comparing each of the methods of management of a miscarriage for incomplete miscarriage subgroup analysis for the outcome of days of bleeding. Ranking indicates the cumulative probability of being the best method, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the SUrface underneath this Cumulative RAnking line (SUCRA); the larger the SUCRA the higher its rank among all available methods.



Other subgroup analyses

We had planned on performing a subgroup analyses based on gestation of miscarriage, however, only five trials (Machtinger 2002; Machtinger 2004; Nasreen 2009; Sahin 2001; Stockheim 2006) specified a gestational age of less than or equal to nine weeks. The remaining trials did not differentiate between miscarriages of less than or equal to nine weeks or greater than nine weeks but less than or equal to 14 weeks of gestation. Therefore, this analysis was not possible. We had also planned to perform a subgroup analysis of electric versus manual vacuum aspiration for the suction aspiration intervention, however, 12 trials did not explicitly state the method of suction aspiration, one trial (Zhang 2005) included both electric and manual aspiration in their suction aspiration group depending upon which site the patient was treated at and did not differentiate between them. Therefore this left only four trials (Chung 1999; Dangalla 2012; Demetroulis 2001; Kittiwatanakul 2012), which explicitly used electric vacuum aspiration and 15 trials which explicitly used manual vacuum aspiration and network meta-analysis was not possible. We had also planned to perform a subgroup analysis based on type of healthcare setting (inpatient versus outpatient). This was not performed as the healthcare setting was not explicitly stated in the vast majority of trials and many of the interventions appeared to have presented the results combining inpatient and

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

outpatient patients. When describing the interventions, authors made judgements on the healthcare settings for the table of characteristics based on the available descriptions in the trials, but a meaningful subgroup analysis was not possible. We had also planned a subgroup analysis based on the dosage, regimen and route of drug administration for the medical interventions. Whilst most of the trials used mifepristone at a similar dose and a similar route of administration, there was significant heterogeneity in terms of the way misoprostol was used for route, dosage and regimen. For this reason, a network meta-analysis according to the different routes, dosages and regimens of misoprostol was not considered meaningful and was not performed. Finally, we considered performing subgroup analysis for the composite outcome of death and serious complications for the subgroups of missed miscarriage and incomplete miscarriage but only ten and 14 trials, respectively reported the type of miscarriage for this composite outcome and therefore any meaningful network meta-analysis was judged by the authors not to be possible or relevant.

Sensitivity analysis

We carried out pre-specified sensitivity analyses by restricting our analyses to studies at low risk of bias and studies that were placebo-controlled. Sensitivity analyses were also performed according to the choice of relative effect measure (risk ratio (RR) versus odds ratio (OR)) and the statistical model (fixed-effect versus random-effects model). The sensitivity analyses show that the overall results are not affected by the above mentioned criteria or decisions.

DISCUSSION

Summary of main results

This review includes 78 randomised trials involving 17,795 women. Most trials were conducted in hospital settings and included women with missed or incomplete miscarriage. Of the 78 included studies, 92% contributed data to the analysis, 8% did not present the data in a usable form for meta-analysis. Across the 71 trials (158 trial arms), the following methods were used: 33% used misoprostol; 32% used suction aspiration; 16% used expectant management or placebo; 11% used dilatation and curettage; 6% used mifepristone plus misoprostol; and 2% used suction aspiration plus cervical preparation.

Based on relative effects from network meta-analysis of 59 trials (12,591 women), we found that suction aspiration plus cervical preparation, dilatation and curettage, suction aspiration, mifepristone plus misoprostol and misoprostol may be more effective than expectant management or placebo for achieving a complete miscarriage. The highest ranked surgical method was suction aspiration plus cervical preparation. The highest ranked non-surgical method was mifepristone plus misoprostol. All surgical methods were ranked higher than medical methods, which in turn were ranked higher than expectant management or placebo.

Based on relative effects from network meta-analysis of 35 trials (8161 participants), we found that dilatation and curettage, suction aspiration, misoprostol and mifepristone plus misoprostol are compatible with a wide range of treatment effects for death and serious complications when compared with expectant management or placebo. No deaths were reported in the trials that contributed towards this outcome, therefore it was entirely composed of serious complications. The most common serious complications included blood transfusions, uterine perforations, hysterectomies, and intensive care unit admissions. The ranking for most methods was not clear for this outcome due to limited data. However, expectant management or placebo ranked bottom amongst all available methods.

Subgroup analyses revealed important differences for the effectiveness of the available methods for managing the miscarriage according to the type of miscarriage. Specifically, for women with missed miscarriage, relative effects from the network meta-analysis of 16 trials, suggest that dilatation and curettage is more effective in achieving a complete miscarriage compared with expectant management or placebo. Misoprostol, mifepristone plus misoprostol and suction aspiration are probably also more effective in achieving a complete miscarriage compared with expectant management or placebo. For women with incomplete miscarriage, relative effects from the network meta-analysis of 26 trials suggest that misoprostol, dilatation and curettage and suction aspiration are probably more effective in achieving a complete miscarriage compared with expectant management or placebo. Mifepristone plus misoprostol is compatible with a wide range of treatment affects for the outcome of complete miscarriage, when compared with expectant management or placebo. The network meta-analyses for incomplete and missed miscarriages agreed with the overall analysis in that surgical methods were better for providing a definitive treatment for a miscarriage than medical methods, which in turn were better than expectant management/ placebo. However, the relative effects were substantially lessened in women with incomplete miscarriage compared to women with missed miscarriage. Since type of miscarriage (missed and incomplete) appears to be a source of inconsistency and heterogeneity within these data, we acknowledge that the main network meta-analysis may be unreliable. However, we plan to explore this further in future updates and consider the primary analysis as separate networks for missed and incomplete miscarriage.

Overall completeness and applicability of evidence

This network meta-analysis provides the relative effectiveness of all methods used in the management of a miscarriage in a coherent and methodologically robust way across important clinical outcomes by combining both direct and indirect evidence, thus increasing the statistical power and confidence in the results. We found that most of the included trials reported our primary outcome of complete miscarriage and provided enough information to allow us to extract a composite outcome of death and serious complications. Most of our secondary outcomes were also reported in enough trials to perform network meta-analysis. This increased the power across most of our analyses and contributed to the consistency in the rankings across all outcomes related to complete miscarriage such as need for unplanned or emergency surgical procedures, readmissions to hospital and days of bleeding.

We were able to evaluate the impact of the type of miscarriage on the rankings and relative effectiveness of each method of miscarriage management. A high level of statistical inconsistency and heterogeneity was identified within the evidence, therefore subgroup analyses were performed for incomplete and missed miscarriage. Rankings within the subgroups were comparable to the overall rankings. For both incomplete and missed miscarriages, the surgical methods were ranked higher than the medical methods, which in turn were ranked higher than the expectant

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

management or placebo. However, we did find important differences in the effectiveness of the surgical and medical options amongst the two subgroups of women. The relative benefits for women with missed miscarriages undergoing any management method other than expectant management or placebo were far greater compared to women with incomplete miscarriages. This is probably because expectant management or placebo is more likely to be a more effective management option when the process of miscarriage has already started.

Unfortunately, not enough of the included trials differentiated between other effect modifiers such as gestational age of the miscarriage, healthcare setting of the intervention was not clearly stated in most trials and there was too much heterogeneity with regard to different dosages, regimens and routes of drug administration for meaningful results from network meta-analysis. This was particularly the case with misoprostol and the misoprostol component of mifepristone and misoprostol. Misoprostol depending on the trial was administered orally, vaginally or sublingually, at a dose of 400 mcg or 600 mcg or 800 mcg as a one-off dose, every four hours or six hours or on a following day (see Characteristics of included studies).

All the trials had wide inclusion criteria, none of the trials had restrictions on age or body mass index or ethnicity. Trials were also conducted across 37 countries, in a mix of high-, middle- and low-income countries from North America, South America, Europe, Africa and all over Asia. Trials were performed in a wide variety of settings from local clinics to district hospitals and in large tertiary and university hospitals. Many of the trials conducted in low- and middle-income countries also included women who may have had incomplete termination care who presented at inclusion as incomplete miscarriage (Characteristics of included studies). All of this ensures applicability of the evidence worldwide, to any women seeking treatment for a miscarriage of less than or equal to 14 weeks gestation in any healthcare setting including women whose miscarriage may have been induced medically. Both mifepristone and misoprostol are listed in the WHO Model list of essential medicines 2019 (WHO 2019). A vaginal speculum and surgical suction pump (manual or electric) with catheter (which is the basis of suction aspiration) are on the WHO generic essential emergency equipment list (WHO 2012) ensuring they are available around the world for most healthcare settings.

Quality of the evidence

We recognise that there is no single established approach for assessing the certainty of the effect estimates generated by the network meta-analysis. We applied the rigorous method for appraising the certainty of network evidence as proposed by the GRADE Working group. Overall, the evidence presented varied widely in certainty, and our confidence in the effect estimates ranged from very low to moderate certainty. When we compared the five other methods of miscarriage management versus expectant management or placebo, the certainty of network level evidence for the outcome of complete miscarriage, was either moderate or low. For suction aspiration plus cervical preparation being ranked first, the certainty was low due to downgrading of the indirect evidence for limitations in study design. For dilatation and curettage, suction aspiration and misoprostol being ranked second, third and fifth, the certainty of network level evidence was low due to moderate certainty direct evidence and inconsistency between direct and indirect estimates. The certainty of network level evidence was moderate for mifepristone plus misoprostol (Summary of findings 1). Evidence for suction aspiration versus misoprostol for the outcomes of nausea, vomiting and diarrhoea were downgraded for publication bias. The certainty of evidence is also affected by inconsistencies between how different studies have reported outcomes.

The GRADE certainty of evidence assessment for the network meta-analysis for the composite outcome of death and serious complications when comparing the five other methods to expectant management or placebo was low. There was downgrading either due to low certainty direct evidence (no intransitivity or incoherence) or due to low certainty indirect evidence (no intransitivity or incoherence) (Summary of findings 4).

The risk of bias of the individual studies which contributed to this network meta-analysis varied, but the majority were judged to be at low risk of bias which included large, well-conducted and methodologically robust trials (Figure 3). Overall therefore, we feel the risk of bias was low and the sensitivity analysis removing high risk of bias trials, confirmed our conclusion.

Potential biases in the review process

Four of the review authors (AC, AJD, IDG and LB) were involved with the MifeMiso trial (Chu 2020). None of these authors participated in any decisions regarding this trial (i.e. assessment for inclusion/exclusion, trial quality, data extraction) for the purposes of this review or for future updates – these tasks have been carried out by other members of the team who were not directly involved in the trial. The certainty of the evidence was assessed by a team of authors based in different countries. Before we could GRADE the network meta-analysis evidence, we had to determine the methodology for this process because there is no well-established approach or accompanying tools such as software. All GRADE assessments were undertaken independently by two individuals (JG and AP) and then re-assessed independently by a third review author (IDG) who was the arbiter of any disagreements.

The included studies did vary according to when they were conducted. The earliest was in 1979 (Caceres 1979), with a further study conducted in 1981 by the same author (Caceres 1981); nine studies were published in the decade beginning 1990; 32 were published in the decade beginning 2000; and 27 were published in the decade beginning 2010. The actual interventions are unlikely to have changed significantly during this time, however, the general care women receive may well have done, with improvements to efforts used to control side effects such as pain, nausea and vomiting. However, overall 59 out of 70 trials were conducted since 2000 and therefore we believe that there is minimal impact on the network meta-analysis from this.

A source of heterogeneity and inconsistency was the type of miscarriage as discussed before that we plan to explore this further in future updates and consider the primary analysis as separate networks for missed and incomplete miscarriage.

A further source of heterogeneity was differences in how the primary outcome of complete miscarriage was assessed with some trials assessing the complete miscarriage outcome clinically based on history and examination, whilst others used a combination of ultrasonography to check for an empty uterine cavity and clinical assessment. Another source of heterogeneity was the time

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

point used to assess complete miscarriage. Removing trials which only used clinical examination or ultrasonography, or limiting the analysis to studies that used a specific time point to assess complete miscarriage would have greatly reduced the number of trials available for the network meta-analysis and hence reduced the strength of our overall findings. Lastly, not all trials reported data on side effects and severity of side effects, hence these analyses were often underpowered or network meta-analysis was not possible.

Agreements and disagreements with other studies or reviews

There are four Cochrane Reviews listed in the treatment of miscarriage section for the Pregnancy and Childbirth group which are comparable to this review, (Lemmers 2019; Kim 2017; Nanda 2012; Tuncalp 2010). Lemmers 2019 compared misoprostol (with various routes of administration), mifepristone and vaginal gemeprost with surgical management, expectant management, placebo or other different types of medical intervention for miscarriages up to 24 weeks of gestation. Our results agreed that misoprostol was better than placebo and expectant management in accomplishing a complete miscarriage, but less effective when compared to surgical management. Kim 2017 compared vaginal misoprostol with expectant management and misoprostol via any route of administration with surgical evacuation for incomplete miscarriage. Our results agreed that misoprostol was less effective at completing a miscarriage compared to surgical methods. Kim 2017 found no difference when comparing misoprostol with expectant care (based on two studies, 150 women) whereas we found a difference when comparing misoprostol with expectant management or placebo (based on nine studies, 755 women). Nanda 2012 compared expectant management with surgical management for management of a miscarriage. Our results agreed with this review that expectant management was more likely to result in an incomplete miscarriage and that there was a higher need for unplanned surgical treatment with expectant management when compared to surgical management. Tuncalp 2010 compared suction aspiration with dilatation and curettage. Our results agreed with this review that suction aspiration was associated with decreased blood loss when compared with dilatation and curettage. A similar network meta-analysis on this has previously been conducted (Al Wattar 2019), which concluded that medical treatments for first-trimester miscarriage have similar effectiveness and side effects compared to surgery. The scope of this review was much smaller, with only 46 trials included, which resulted in lower power and may account for the different conclusion reached.

AUTHORS' CONCLUSIONS

Implications for practice

This review shows that all medical and surgical methods for managing a miscarriage were more effective than when compared with expectant management, based on moderate- and low-certainty evidence. Expectant management has the lowest chance of successfully managing a miscarriage and has the highest chance of serious complications and the need for unplanned or emergency surgery. This review adds to the evidence base that surgical and medical methods for managing miscarriage appear to be more beneficial in women with missed miscarriage compared to women with incomplete miscarriage. However, the evidence suggests that surgical treatment of a miscarriage does carry higher risks of pelvic infection compared to medical and expectant options and that medical options are probably the worst for side effects such as nausea, vomiting, diarrhoea and pyrexia. Policy makers should take into account the various options when considering implementation strategies, building or supporting health service delivery and healthcare providers should take into account the type of miscarriage when making decisions about the management of miscarriage. Healthcare providers should inform women about the risks and benefits for each method according to the type of miscarriage, and take into account their preferences for management options with similar risks and benefits.

Implications for research

The majority of the evidence presented in this review are of low certainty. Further high-quality trials are required to improve the certainty of the evidence. Many of the outcomes of this review are not routinely reported and future trials should report serious complications such as blood transfusions, infection, mean volumes of blood loss, changes in haemoglobin measurement before and after the miscarriage, mean durations of hospital stay, readmission to hospital consistently. This is especially the case for patient-reported outcomes such as pain scores, days of bleeding, women's views or satisfaction, nausea, vomiting, diarrhoea, anxiety and depression scores.

Future trials should examine the effectiveness of the methods of miscarriage separate for the subgroups of women according to their type of miscarriage. Trials could have broad inclusion criteria, including women both with missed or incomplete miscarriage, but effectiveness results should be presented separately for type of miscarriage. There is likely to be wider availability of the medical management of miscarriage options due to the nature of the surgical interventions requiring specialist equipment and training and therefore further work is needed to establish the most effective doses, routes and regimens of misoprostol and the misoprostol component for mifepristone plus misoprostol as this current network meta-analysis does not establish this. There is paucity of data regarding cervical preparation before surgical management, and the combination of mifepristone plus misoprostol so future trials should try to address this.

Future trials should also examine the impact of longer-term sequelae of methods of miscarriage management such as time to return to normal menstruation and future fertility rates to provide additional information to women when counselling about treatment options as this information is often a priority for women. This information was not widely available in the included papers for this current review, but should be considered for inclusion in a future update if and when sufficient evidence becomes available. A uniform core outcome set for miscarriage would also aid any future evidence synthesis.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this review has been commented on by five peers (an editor, and one referee who is external to the editorial team), our Group's consumer editor, our Group's Statistical Adviser, Cochrane Methods and Cochrane Children and Families' Associate Editor. The review authors are grateful to the following peer reviewers for their

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

time and comments: Dr Rui Wang, Department of Obstetrics and Gynaecology, Monash University, Australia.

This project was supported by the Tommy's National Centre for Miscarriage Research and the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Pregnancy and Childbirth Group. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, the NIHR, the NHS or the Department of Health and Social Care.

Malcolm J Price is supported by the NIHR Birmingham Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, NIHR or the Department of Health and Social Care.

The World Health Organization (WHO) and Jayasish Ghosh, Argyro Papadopoulou, Hannah Jeffery, Adam Devall, Leanne Beeson, Vivian Do, Malcolm J Price, Aurelio Tobias, A Metin Gülmezoglu, Arri Coomarasamy, Ioannis D Gallos, retain copyright and all other rights in their respective contributions to the manuscript of this Cochrane Review as submitted for publication.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

REFERENCES

References to studies included in this review

Abdelaleem 2020 *{published data only}*

Abdelaleem MA, Ali MK, Emam S, Abbas AM. Medical versus expectant management in women with incomplete first-trimester miscarriage initially treated with misoprostol: a randomized controlled study. Fertility and Sterility (first received 2020);**114**(3):e46. [CENTRAL: CN-02193128] [EMBASE: 2008033880]

Al-Maani 2014 *{published data only}*

Al-Maani W, Solomayer E, Hammadeh M. Expectant versus surgical management of first-trimester miscarriage: a randomised controlled study. *Archives of Gynecology and Obstetrics* 2014;**289**(5):1011-5.

Ara 2009 *{published data only}*

Ara G, Nargis S, Khatun R, Saha A. Vaginal misoprostol as a medical management in early pregnancy loss. *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S533-4.

Arellano 2009 *{published data only}*

Arellano M, Durocher J, Leon W, Montesinos R, Pena M, Winikoff B. Introduction of misoprostol for incomplete abortion care in Latin America: evidence from Ecuador. *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S49.

Arif 2018 *{published data only}*

Arif Butt T, Iqbal A, Saeed M, Ousuf IY, Murtaza A. Outcomes of manual vacuum aspiration versus dilatation and curettage in first trimester miscarriages. *Pakistan Journal of Medical and Health Sciences* 2018;**12**(2):611-3.

Bagratee 2004 *{published data only}*

Bagratee JS, Khullar V, Regan L, Moodley J, Kagoro H. A randomized controlled trial comparing medical and expectant management of first trimester miscarriage. *Human Reproduction* 2004;**19**(2):266-71.

Bique 2007 *{published data only}*

Bique C, Usta M, Debora B, Chong E, Westheimer E, Winikoff B. Comparison of misoprostol and manual vacuum aspiration for the treatment of incomplete abortion. *International Journal of Gynecology & Obstetrics* 2007;**98**(3):222-6.

Blohm 2005 *{published data only}*

Blohm F, Friden BE, Milsom I, Platz-Christensen JJ, Nielsen S. A randomised double blind trial comparing misoprostol or placebo in the management of early miscarriage. *BJOG: an international journal of obstetrics and gynaecology* 2005;**112**(8):1090-5.

Braham 2016 *{published data only}*

Braham R. The use of misoprostol for first time spontaneous abortion. *West Indian Medical Journal* 2016;**65**(Suppl 5):74.

Caceres 1979 *{published data only}*

Caceres EM. Manangement of incomplete abortion: completion by vacuum aspiration and by sharp curettage. Personal communication 1979.

Caceres 1981 *{published data only}*

Caceres GH, Gamboa GR, Hernandez MA, Escobar GL. Hospital management of incomplete abortion: comparative study of dilation and curettage versus vacuum aspiration [Manejo hospitalario del aborto incompleto: Estudio Comparitivo del curetaje uterino versus la]. Personal communication 1981:1.

Chigbu 2012 *{published data only}*

Chigbu B, Onwere S, Aluka C, Kamanu C, Ezenobi O. Is misoprostol a suitable alternative to the surgical evacuation of incomplete abortion in rural South-Eastern Nigeria? *East African Medical Journal* 2012;**89**(5):172-7.

Chipchase 1997 *{published data only}*

Chipchase J, James D. Randomised trial of expectant versus surgical management of spontaneous miscarriage. *British Journal of Obstetrics and Gynaecology* 1997;**104**(7):840-1.

Chu 2020 *{published data only}*

Chu JJ, Devall AJ, Gallos ID, Coomarasamy A, Beeson LE, Hardy P, et al. Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): a randomised, double-blind, placebo-controlled trial. *Lancet (london, England)* 2020 Sep 12;**396**(10253):770-8. [CENTRAL: CN-02174259] [EMBASE: 2010584315] [PMID: 32853559]

Chung 1997 *{published data only}*

Chung TK, Cheung LP, Haines CJ. Spontaneous abortion: a randomized controlled trial of misoprostol versus routine surgical evacuation. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**(167):72.

Chung 1999 *{published data only}*

Chung TK, Cheung LP, Lee D, Haines CJ. Spontaneous abortion: a randomized controlled trial of misoprostol versus routine uterine curettage. *British Journal of Obstetrics and Gynaecology* 1998;**105**(Suppl 17):127.

Chung TK, ISRCTN43067169. A randomised, controlled clinical trial involving women who have aborted spontaneously; the health, social and operational costs, outcomes of conservative and routine management. http://www.isrctn.com/ISRCTN43067169 2002.

* Chung TK, Lee DT, Cheung LP, Haines CJ, Chang AM. Spontaneous abortion: a randomised controlled trial comparing surgical evacuation with conservative management using misoprostol. *Fertility and Sterility* 1999;**71**(6):1054-9.

Chung TK, Lee DT. A randomised controlled clinical trial involving women who have aborted spontaneously: the health, social and operational cost outcomes of conservative and routine management protocols. Personal communication 1998.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Dabash 2010 *{published data only}*

Dabash R, Cherine M, Darwish E, Blum J, Hassanein N, Abdel Daiem T, et al. Bleeding following surgical (MVA) and medical (400 ug sublingual misoprostol) treatment of incomplete abortion. *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S150-1.

* Dabash R, Ramadan MC, Darwish E, Hassanein N, Blum J, Winikoff B. A randomized controlled trial of 400-mug sublingual misoprostol versus manual vacuum aspiration for the treatment of incomplete abortion in two Egyptian hospitals. *International Journal of Gynecology & Obstetrics* 2010;**111**(2):131-5.

Ramadan MC. Misoprostol versus MVA for incomplete abortion: results from a randomized controlled trial in Egypt. *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S68-9.

Dangalla 2012 *{published data only}*

Dangalla DP, Goonewardene IM. Surgical treatment versus expectant care in the management of incomplete miscarriage: a randomised controlled trial. *Ceylon Medical Journal* 2012;**57**(4):140-5.

Dao 2007 *{published data only}*

Dao B, Blum J, Thieba B, Raghavan S, Ouedraego M, Lankoande J, et al. Is misoprostol a safe, effective and acceptable alternative to manual vacuum aspiration for postabortion care? Results from a randomised trial in Burkina Faso, West Africa. *BJOG: an international journal of obstetrics and gynaecology* 2007;**114**(11):1368-75.

Das 2014 *{published data only}*

Das CM, Sharma M, Pardeep K, Khurshid F. To compare the safety and efficacy of manual vacuum aspiration with misoprostol (ST mom) 600mg in incomplete miscarriage. *Journal of the Liaquat University of Medical and Health Sciences* 2014;**13**(3):93-6. [CENTRAL: CN-01086151] [EMBASE: 605161649]

Davis 2007 *{published data only}*

Davis AR, Hendlish SK, Westhoff C, Frederick MM, Zhang J, Gilles JM, et al. Bleeding patterns after misoprostol vs surgical treatment of early pregnancy failure: results from a randomized trial. *American Journal of Obstetrics and Gynecology* 2007;**196**(1):31.

de Holanda 2003 *{published data only}*

de Holanda AA, dos Santos HP, Barbosa MF, Barreto CF, Felinto AS, de Araujo IA. Treatment of miscarriage in the first trimester of pregnancy: curettage versus manual vacuum aspiration [Tratamento do abortamento do primeiro trimestre da gestacao: curetagem versus aspiracao manual a vacuo]. *Revista Brasileira de Ginecologia e Obstetricia* 2003;**25**(4):271-6.

de Jonge 1995 *{published data only}*

de Jonge ET, Makin JD, Manefeldt E, De Wet GH, Pattinson RC. Randomised clinical trial of medical evacuation and surgical curettage for incomplete miscarriage. *BMJ* 1995;**311**(7006):662.

Demetroulis 2001 *{published data only}*

* Demetroulis C, Saridogan E, Kunde D, Naftalin AA. A prospective randomized control trial comparing medical and surgical treatment for early pregnancy failure. *Human Reproduction* 2001;**16**(2):365-9.

Demetroulis C, Saridogan E, Kunde D, Naftalin AA. A prospective randomized control trial comparing medical and surgical treatment for early pregnancy failure [abstract]. *XVI FIGO World Congress of Obstetrics & Gynecology; 2000 Sept 3-8; Washington DC, USA* 2000;**Book 3**:69.

Fernlund 2018 *{published data only}*

Fernlund A, Jokubkiene L, Sladkevicius P, Valentin L. A randomised controlled trial comparing misoprostol to expectant care in early pregnancy failure. *Ultrasound in Obstetrics & Gynecology* 2017;**50**(Suppl 1):15, Abstract no: OC08.03.

* Fernlund A, Jokubkiene L, Sladkevicius P, Valentin L. Misoprostol treatment vs expectant management in women with early non-viable pregnancy and vaginal bleeding: a pragmatic randomized controlled trial. *Ultrasound in Obstetrics & Gynecology* 2018;**51**(1):24-32.

Fernlund A, Jokubkiene L, Sladkevicius P, Valentin L. Predictors of complete miscarriage after expectant management or misoprostol treatment of non-viable early pregnancy in women with vaginal bleeding. *Archives of Gynecology and Obstetrics* 2020 Jul 7;**302**(5). [CENTRAL: CN-02140210] [EMBASE: 2005498459] [PMID: 32638095]

Valentin L. Which is the optimal treatment for miscarriage with a gestational sac in the uterus and which factors can predict if the treatment will be successful? clinicaltrials.gov/ct2/show/NCT01033903 (first received: 16 December 2009).

Fonseca 1997 *{published data only}*

Fonseca W, Misago C, Fernandes L, Correia L, Silveira D. Use of manual vacuum aspiration in reducing cost and duration of hospitalization due to incomplete abortion in an urban area of northeastern brazil [Uso da aspiracao manual a vacuo na reducao do custo e duracao de internamentos por aborto incompleto em fortaleza, CE, Brasil]. *Revista de Saude Publica* 1997;**31**(5):472-8.

Ganguly 2010 *{published data only}*

Ganguly RP, Mukhopadhyay S, Burman SK, Patra KK, Jha T, Mukherji J. A randomized trial of misoprostol compared with manual vacuum aspiration for early pregnancy failure. *Nepal Journal of Obstetrics and Gynaecology* 2010;**5**(2):8-13.

Gazvani 2000 *{published data only}*

Gazvani R, Templeton A. A pilot study for the use of manual vacuum aspiration in early pregnancy loss. *Journal of Obstetrics and Gynaecology* 2000;**20**(1):105.

Graziosi 2004 *{published data only}*

Graziosi GC, Bruinse HW, Reuwer PJH, van Kessel PH, Westerweel PE, Mol BW. Misoprostol versus curettage in women with early pregnancy failure: impact on women's health-related

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

quality life. A randomized controlled trial. *Human Reproduction* 2005;**20**(8):2340-7.

Graziosi GC, van der Steeg JW, Reuwer PH, Drogtrop AP, Bruinse HW, Mol BW. Economic evaluation of misoprostol in the treatment of early pregnancy failure compared to curettage after an expectant management. *Human Reproduction* 2005;**20**(4):1067-71.

* Graziosi GCM, Mol BW, Reuwer PJH, Drogtrop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. *Human Reproduction* 2004;**19**(8):1894-9.

Hamel 2021 *{published data only}*

* Hamel C, Coppus S, van den Berg J, Hink E, van Seeters J, van Kesteren P, et al. Mifepristone followed by misoprostol compared with placebo followed by misoprostol as medical treatment for early pregnancy loss (the TripleM trial): A double-blind placebo-controlled randomised trial. EClinicalMedicine 2021:https://doi.org/10.1016/j.eclinm.2020.100716.

van den Berg J, Hamel CC, Snijders MP, Coppus SF, Vandenbussche FP. Mifepristone and misoprostol versus misoprostol alone for uterine evacuation after early pregnancy failure: study protocol for a randomized double blinded placebo-controlled comparison (Triple M Trial). *BMC Pregnancy and Childbirth* 2019;**19**(1):443. [CENTRAL: CN-02012095] [EMBASE: 630004464] [PMID: 31775677]

Harwood 2008 *{published data only}*

Harwood B, Nansel T, for theNIofCHandHDMofEPFT. Quality of life and acceptability of medical versus surgical management of early pregnancy failure. *BJOG: an international journal of obstetrics and gynaecology* 2008;**115**(4):501-8.

Ibiyemi 2018 *{published data only}*

Ibiyemi K F, Ijaiya M A, Adesina KT. Randomised trial of oral misoprostol versus manual vacuum aspiration for the treatment of incomplete abortion at a Nigerian Tertiary Unit. *Sultan Qaboos University Medical Journal* 2019;**19**:38-43.

* Ibiyemi KF, PACTR201803003087264. Randomised trial of oral misoprostol versus manual vacuum aspiration for treatment of incomplete abortion in a Nigerian Tertiary hospital. https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=3087 2018.

Igogo 2015 *{published data only}*

Igogo P, Karanja J, Kamau K, Tamooh H. Use of misoprostol for incomplete abortion in resource-poor settings. *Contraception* 2015;**92**(4):370.

Kaluaarachchi 2015 *{published data only}*

Kaluaarachchi A, Kopalakrishnan M. Surgical, medical or expectant management of first trimester miscarriage and its implications on clinical and psychological outcomes –a randomized controlled trial. *Sri Lanka Journal of Obstetrics and Gynaecology* 2015;**37**(Suppl 1):17, Abstract no: OP 39.

Karlsen 2001 *{published data only}*

Karlsen JH, Schiotz HA. Curettage or not after spontaneous abortion? [Norwegian] [Utskrapning eller ikke etter spontanabort?]. *Tidsskrift for Den Norske Laegeforening* 2001;**121**(24):2812-4.

Kashif 2020 *{published data only}*

Kashif A, Faisal J, Jawad Z, Inayat FC, Shabana N, Kanwal S. Comparison of vaginal misoprostol with suction evacuation for the management of first trimester spontaneous miscarriage. *Pakistan Journal of Medical and Health Sciences* 2020;**14**(2):517-21. [CENTRAL: CN-02193578] [EMBASE: 2007799407]

Kittiwatanakul 2012 *{published data only}*

Kittiwatanakul W, Weerakiet S. Comparison of efficacy of modified electric vacuum aspiration with sharp curettage for the treatment of incomplete abortion: randomized controlled trial. *Journal of Obstetrics and Gynaecology Research* 2012;**38**(4):681-5.

Kong 2013 *{published data only}*

Kong GW, Lok IH, Yiu AK, Hui AS, Lai BP, Chung TK. Clinical and psychological impact after surgical, medical or expectant management of first-trimester miscarriage - a randomised controlled trial. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 2013;**53**(2):170-7.

Kovavisarach 2002 *{published data only}*

* Kovavisarach E, Sathapanachai U. Intravaginal 400 micrograms misoprostol for pregnancy termination in cases of blighted ovum: a randomised controlled trial. *Australian & New Zealand Journal of Obstetrics and Gynaecology* 2002;**42**(2):161-3.

Sathapanachai U. Intravaginal 400 micrograms misoprostol for pregnancy termination in cases of blighted ovum. *Thai Journal of Obstetrics and Gynaecology* 2000;**12**(4):363.

Kyaw 2015 *{published data only}*

Kyaw O, Yi KH, Thida M. A comparison of medical evacuation using single dose vaginal misoprostol (800mug) versus surgical evacuation in management of early pregnancy loss in North Okkalapa General and Teaching Hospital, Yangon. *Journal of Obstetrics and Gynaecology Research* 2015;**41**:3, Abstract no: YGA O 06.

Lee 2001 *{published data only}*

Lee DT, Cheung LP, Haines CJ, Chan KP, Chung TK. A comparison of the psychologic impact and client satisfaction of surgical treatment with medical treatment of spontaneous abortion: a randomized controlled trial. *American Journal of Obstetrics and Gynecology* 2001;**185**:953-8.

Lister 2005 *{published data only}*

Lister MS, Shaffer LE, Bell JG, Lutter KQ, Moorma KH. Randomized, double-blind, placebo-controlled trial of vaginal misoprostol for management of early pregnancy failures. *American Journal of Obstetrics and Gynecology* 2005;**193**:1338-43.

Machtinger 2002 *{published data only}*

Machtinger R, Stockheim D, Goldenberg M, Soriano D, Atlas M, Seidman DS. A randomized prospective study of misoprostol alone or combined with mifepristone for treatment of first

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

trimester spontaneous abortion [abstract]. *Fertility and Sterility* 2002;**78**(3 Suppl 1):S64.

Machtinger 2004 *{published data only}*

Machtinger R, Stockheim D, Shulman A, Dulitzki M, Schiff E, Seidman DS. A randomized prospective study comparing the effectiveness of four protocols for treatment of first trimester spontaneous abortion [abstract]. *Fertility and Sterility* 2004;**82 Suppl 2**:S80.

Montesinos 2011 *{published data only}*

* Montesinos R, Durocher J, Leon W, Arellano M, Pena M, Pinto E, et al. Oral misoprostol for the management of incomplete abortion in Ecuador. *International Journal of Gynecology & Obstetrics* 2011;**115**(2):135-9.

NCT00674232. Misoprostol for treatment of incomplete abortion. https://clinicaltrials.gov/ct2/show/NCT00674232 2008.

Moodliar 2005 *{published data only}*

Moodliar S, Bagratee JS, Moodley J. Medical vs. surgical evacuation of first-trimester spontaneous abortion. *International Journal of Gynecology & Obstetrics* 2005;**91**:21-6.

Muffley 2002 *{published data only}*

Muffley PE, Stitely ML, Gherman RB. Early intrauterine pregnancy failure: a randomized trial of medical versus surgical treatment. *American Journal of Obstetrics and Gynecology* 2002;**187**:321-6.

Nadarajah 2014 *{published data only}*

* Nadarajah R, Quek YS, Kuppannan K, Woon SY, Jeganathan R. A randomised controlled trial of expectant management versus surgical evacuation of early pregnancy loss. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 2014;**178**:35-41.

Quek YS, Woon SY, Ravichandran N, Ravichandran J. A randomised controlled trial of expectant management versus surgical evacuation of early pregnancy loss. *BJOG: an international journal of obstetrics and gynaecology* 2012;**119**(Suppl 1):218.

Nasreen 2009 *{published data only}*

Nasreen Z. What for early pregnancy failure manual vacuum aspiration (MVA) with small dose misoprostol or misoprostol alone? *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S539-40.

Ngai 2001 *{published data only}*

Ngai SW, Chan YM, Tang OS, Ho PC. Vaginal misoprostol as medical treatment for first trimester spontaneous miscarriage. *Human Reproduction* 2001;**16**(7):1493-6.

Nielsen 1995 *{published data only}*

Nielsen S, Hahlin M, Moller A, Granberg S. Bereavement, grieving and psychological morbidity after first trimester spontaneous abortion: comparing expectant management with surgical evacuation. *Human Reproduction* 1996;**11**(8):1767-70.

* Nielsen S, Hahlin M. Expectant management of first-trimester spontaneous abortion [see comments]. *Lancet* 1995;**345**(8942):84-6.

Nielsen 1999 *{published data only}*

Nielsen S, Hahlin M, Platz-Christensen J. Expectant management or pharmacological treatment for first trimester spontaneous abortion: a randomised trial. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**(167):77.

* Nielsen S, Hahlin M, Platz-Christensen J. Randomised trial comparing expectant with medical management for first trimester miscarriages. *British Journal of Obstetrics and Gynaecology* 1999;**106**(8):804-7.

Nielsen S, Hahlin M. Expectant management of first-trimester miscarriage. In: Grundzinkas JG, editors(s). Problems in Early Pregnancy - Advances in Diagnosis and Management. London: RCOG, 1997:265-76.

Niinimaki 2006 *{published data only}*

* Niinimaki M, Jouppila P, Martikainen H, Talvensaari-Mattila A. A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. *Fertility and Sterility* 2006;**86**(2):367-72.

Niinimaki M, Karinen P, Hartikainen AL, Pouta A. Treating miscarriages: a randomised study of cost-effectiveness in medical or surgical choice. *BJOG: an international journal of obstetrics and gynaecology* 2009;**116**(7):984-90.

Nwafor 2020 *{published data only}*

Nwafor JI, Agwu UM, Egbuji CC, Ekwedigwe KC. Misoprostol versus manual vacuum aspiration for treatment of first-trimester incomplete miscarriage in a low-resource setting: a randomized controlled trial. *Nigerian Journal of Clinical Practice* 2020 May;**23**(5):638-46. [CENTRAL: CN-02122567] [EMBASE: 631677586] [PMID: 32367870]

Patua 2013 *{published data only}*

Patua B, Dasgupta M, Bhattacharyya SK, Bhattacharya S, Hasan SH, Saha S. An approach to evaluate the efficacy of vaginal misoprostol administered for a rapid management of first trimester spontaneous onset incomplete abortion, in comparison to surgical curettage. *Archives of Gynecology and Obstetrics* 2013;**288**(6):1243-8.

Pereira 2006 *{published data only}*

Pereira PP, Oliveira AL, Cabar FR, Armelin AR, Maganha CA, Zugaib M. Comparative study of manual vacuum aspiration and uterine curettage for treatment of abortion. *Revista Da Associacao Medica Brasileira* 2006;**52**(5):304-7.

Phusaanantakul 2010 *{published data only}*

Phusaanantakul P, Promsonthi P, Chanrachakul B. Effect of isosorbide mononitrate for cervical ripening before surgical termination of pregnancy in the first trimester. *International Journal of Gynecology & Obstetrics* 2010;**110**(2):145-8.

Sahin 2001 *{published data only}*

Sahin HG, Sahin HA, Kocer M. Randomized outpatient clinical trial of medical evacuation and surgical curettage in incomplete

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

miscarriage. *European Journal of Contraception & Reproductive Health Care* 2001;**6**(3):141-4.

Salam 2016 *{published data only}*

Salam R, Neelofer R, Naserullah P. Comparative study of manual vacuum aspiration and dilatation & evacuation for the surgical management of early miscarriages: a randomized controlled trial. *Pakistan Journal of Medical and Health Sciences* 2016;**10**(1):183-5.

Schreiber 2018 *{published data only}*

Flynn AN, Roe AH, Koelper N, McAllister A, Sammel MD, Schreiber CA. Timing and efficacy of mifepristone pretreatment for medical management of early pregnancy loss. *Contraception* 2021;**103**(6):404-7. [CENTRAL: CN-02218404] [EMBASE: 2010804683] [PMID: 33476659]

Nagendra D, Koelper N, Loza-Avalos SE, Sonalkar S, Chen M, Atrio J, et al. Cost-effectiveness of mifepristone pretreatment for the medical management of nonviable early pregnancy: secondary analysis of a randomized clinical trial. *JAMA Network Open* 2020 Mar 02;**3**(3):e201594. [CENTRAL: CN-02100126] [EMBASE: 631375356] [PMID: 32215633]

Nagendra D, Schreiber CA, Koelper N, Sonalkar S, Loza-Avalos S, Harvie H. Cost effectiveness of mifepristone pretreatment for the medical management of nonviable early pregnancy. *Obstetrics and Gynecology* 2019;**133**(Suppl 1):6. [EMBASE: L633843717]

NCT02012491. Comparative effectiveness of pregnancy failure management regimens. Https://clinicaltrials.gov/show/nct02012491 2013.

* Schreiber CA, Sonalkar S, Barnhart KT, Ratcliffe SJ, Creinin MD, Atrio J. Mifepristone pretreatment for the medical management of early pregnancy loss. *New England Journal of Medicine* 2018;**378**(23):2161-70.

Sonalkar S, Koelper N, Creinin MD, Atrio JM, Sammel MD, McAllister A, et al. Management of early pregnancy loss with mifepristone and misoprostol: clinical predictors of success from a randomized trial. *American Journal of Obstetrics and Gynecology* 2020;**223**(4):551.e1-551.e7. [CENTRAL: CN-02123177] [EMBASE: 2005910040] [PMID: 32305259]

Schwarzler 2003 *{published data only}*

Schwarzler P. The conservative management of first trimester miscarriages and the use of sonography for patients' selection [abstract]. *Ultrasound in Obstetrics & Gynecology* 2003;**22**(Suppl 1):4.

Shaheen 2017 *{published data only}*

Shaheen H, Khosa MS, Hanif H. Comparison of efficacy of manual vacuum aspiration (MVA) and medical treatment in the management of first trimester missed miscarriage. *Pakistan Journal of Medical and Health Sciences* 2017;**11**(1):270-3.

Shaikh 2008 *{published data only}*

Shaikh ZA. Comparison between misoprostol alone and misoprostol with manual vacuum aspiration for the treatment of missed and incomplete miscarriage. *BJOG: an international journal of obstetrics and gynaecology* 2008;**115**(s1):83.

Shelley 2005 *{published data only}*

Shelley JM, Healy D, Grover S. A randomised trial of surgical, medical and expectant management of first trimester spontaneous miscarriage. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2005;**45**:122-7.

Shuaib 2013 *{published data only}*

Shuaib AA, Alharazi AH. Medical versus surgical termination of the first trimester missed miscarriage. *Alexandria Journal of Medicine* 2013;**49**:13-6.

Shwekerela 2007 *{published data only}*

Shwekerela B, Kalumuna R, Kipingili R, Mashaka N, Westheimer E, Clark W, et al. Misoprostol for treatment of incomplete abortion at the regional hospital level: results from Tanzania. *BJOG: an international journal of obstetrics and gynaecology* 2007;**114**(11):1363-7.

Sinha 2018 *{published data only}*

Sinha P, Suneja A, Guleria K, Aggarwal R, Vaid NB. Comparison of mifepristone followed by misoprostol with misoprostol alone for treatment of early pregnancy failure: a randomized double-blind placebo-controlled trial. *Journal of Obstetrics and Gynecology of India* 2018;**68**(1):39-44.

Stockheim 2006 *{published data only}*

Stockheim D, Machtinger R, Wiser A, Dulitzky M, Soriano D, Goldenberg M, et al. A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. *Fertility and Sterility* 2006;**86**(4):956-60.

Tationo 2012 *{published data only}*

Tationo SH, Ravichandran J, Othman MS. Manual vacuum aspirator versus surgical curettage for surgical treatment of first trimester incomplete miscarriage. *BJOG: an international journal of obstetrics and gynaecology* 2012;**119**(Suppl 1):198.

Taylor 2011 *{published data only}*

Taylor J, Diop A, Blum J, Dolo O, Winikoff B. Oral misoprostol as an alternative to surgical management for incomplete abortion in Ghana. *International Journal of Gynecology & Obstetrics* 2011;**112**(1):40-4.

Torre 2012 *{published data only}*

Rosenberg P//NCT00190294. Comparison expectant with immediate medical management for the evacuation of the no evolutionary pregnancies before 13 GW. clinicaltrials.gov/ct2/show/record/NCT00190294 2006.

* Torre A, Huchon C, Bussieres L, Machevin E, Camus E, Fauconnier A. Immediate versus delayed medical treatment for first-trimester miscarriage: a randomized trial. *American Journal of Obstetrics & Gynecology* 2012;**206**(3):215.e1-6.

Trinder 2006 *{published data only}*

Petrou S, Trinder J, Brocklehurst P, Smith L. Economic evaluation of alternative management methods of first-

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

trimester miscarriage based on results from the MIST trial. *BJOG: an international journal of obstetrics and gynaecology* 2006;**113**(8):879-89.

Smith L, ISRCTN66418282. Randomised controlled trial of expectant, medical and surgical management of early miscarriage. http://www.isrctn.com/ISRCTN66418282 2004.

Smith L. Extension to: randomised controlled trial of expectant, medical and surgical management of early miscarriage. Research Findings Register (www.refer.nhs.uk) (accessed 7 March 2006) 2006.

Smith LF, Ewings PD, Quinlan C. Incidence of pregnancy after expectant, medical, or surgical management of spontaneous first trimester miscarriage: long term follow-up of miscarriage treatment (MIST) randomised controlled trial. *BMJ* 2009;**339**:b3827.

Smith LF, Frost J, Levitas R, Bradley H, Garcia J. Women's experiences of three early miscarriage management options: a qualitative study. *British Journal of General Practice* 2006;**56**(524):198-205.

* Trinder J, Brocklehurst P, Porter R, Read M, Vyas S, Smith L. Management of miscarriage: expectant, medical, or surgical? Results of randomised controlled trial (miscarriage treatment (MIST) trial). *BMJ* 2006;**332**(7552):1235-40.

Ulstrup 1997 *{published data only}*

Ulstrup KS, Lopez HB, Mogensen H, Blaakaer J. Treatment of early spontaneous abortion. Evacuation or expectation? *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76 Suppl**(167:1):78.

Verkuyl 1993 *{published data only}*

Verkuyl DA, Crowther CA. Suction v. conventional curettage in incomplete abortion. A randomised controlled trial [see comments]. *South African Medical Journal* 1993;**83**:13-5.

Weeks 2005 *{published data only}*

Weeks A, Alia G, Blum J, Blanchard K, Winikoff B. A randomised trial of oral misoprostol (600mcg) versus manual vacuum aspiration in the treatment of incomplete miscarriage in Kampala, Uganda. In: 30th British Congress of Obstetrics and Gynaecology; 2004 July 7-9; Glasgow, UK. 2004:27.

* Weeks A, Alia G, Blum J, Winikoff B, Ekwaru P, Durocher J, et al. A randomized trial of misoprostol compared with manual vacuum aspiration for incomplete abortion. *Obstetrics & Gynecology* 2005;**106**(3):540-7.

Wijesinghe 2011 *{published data only}*

Padumadasa S, SLCTR/2008/012. Efficacy of surgical versus expectant management in incomplete miscarriage. https://slctr.lk/trials/slctr-2008-012 2008.

* Wijesinghe PS, Padumadasa GS, Palihawadana TS, Marleen FS. A trial of expectant management in incomplete miscarriage. *Ceylon Medical Journal* 2011;**56**(1):10-3.

Wood 2002 *{published data only}*

Wood SL, Brain PH. Medical management of missed abortion: a randomized clinical trial. *Obstetrics & Gynecology* 2002;**99**(4):563-6.

Zhang 2005 *{published data only}*

Chen BA, Reeves MF, Creinin MD, Gilles JM, Barnhart K, Westhoff C, et al. Misoprostol for treatment of early pregnancy failure in women with previous uterine surgery. *American Journal of Obstetrics & Gynecology* 2008;**198**(6):626.e1-5.

Creinin MD, Huang X, Westhoff C, Barnhart K, Gilles JM, Zhang J, et al. Factors related to successful misoprostol treatment for early pregnancy failure. *Obstetrics & Gynecology* 2006;**107**(4):901-7.

Edwards S, Tureck R, Fredrick M, Huang X, Zhang J, Barnhart K. Patient acceptability of manual versus electric vacuum aspiration for early pregnancy loss. *Journal of Women's Health* 2007;**16**(10):1429-36.

Rausch M, Lorch S, Chung K, Frederick M, Zhang J, Barnhart K. A cost-effectiveness analysis of surgical versus medical management of early pregnancy loss. *Fertility and Sterility* 2012;**97**(2):355-60.e1.

Reeves MF, Lohr PA, Harwood B, Creinin MD. Sonographic findings after misoprostol or vacuum aspiration for early pregnancy failure. *Contraception* 2006;**74**(2):182.

Reeves MF, Lohr PA, Harwood BJ, Creinin MD. Ultrasonographic endometrial thickness after medical and surgical management of early pregnancy failure. *Obstetrics & Gynecology* 2008;**111**(1):106-12.

Zhang J, Gilles J, Barnhart K, Creinin M, Westhoff C, Frederick MM. Medical management with misoprostol for early pregnancy failure: a multicenter, randomized equivalence trial [abstract]. *Fertility and Sterility* 2004;**82 Suppl 2**:S53-4.

* Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM, et al. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. [See comment]. *New England Journal of Medicine* 2005;**353**(8):761-9.

References to studies excluded from this review

Abbasalizadeh 2018 *{published data only}*

Abbasalizadeh F, IRCT2014030114293N1. Comparison the effect of letrozole plus Misoprostol and misoprostol alone in termination of nonviable first trimester pregnancies; a single blinded randomized trial. http://en.irct.ir/trial/13912 2014.

* Abbasalizadeh F, Sahhaf F, Sadeghi-Shabestari P, Mirza-Aghazadeh-Attari M, Naghavi-Behzad M. Comparison between effect of letrozole plus misoprostol and misoprostol alone in terminating non-viable first trimester pregnancies: a single blind randomized trial. *Journal of Family and Reproductive Health* 2018;**12**(1):27-33.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Abdel Fattah 1997 *{published data only}*

Abdel Fattah IH. PGE1 analogue for the induction of midtrimester abortion in cases of intrauterine fetal death. *Acta Obstetricia et Gynecologica Scandinavica Supplement* 1997;**76**(167:2):26.

Abd-El-Maeboud 2012 *{published data only}*

Abd-El-Maeboud KH, Ghazy A, Ibrahim A, Hassan N, El-Bohoty A, Gamal-El-Din I. Vaginal acidity enhancement with a 3% acetic acid gel prior to misoprostol treatment for pregnancy termination in the midtrimester. *International Journal of Gynecology and Obstetrics* 2012;**119**(3):248-52.

Abdelshafy 2019a *{published data only}*

* Abdelshafy A, Awwad H, Abo-Gamra A, Alanwar A, Elkotb AM, Shahin M, et al. Sublingual vs vaginal misoprostol for completion of first trimester missed abortion: a randomised controlled trial. *European Journal of Contraception and Reproductive Health Care* 2019;**24**(2):134-9.

El Shahawy A, NCT02686840. Sublingual versus vaginal misoprostol in medical treatment of first trimestric missed miscarriage: a randomized controlled trial. https://clinicaltrials.gov/ct2/show/NCT02686840 (22 February 2016).

Abediasl 2016 *{published data only}*

Abediasl Z, Sheikh M, Pooransari P, Farahani Z, Kalani F. Vaginal misoprostol versus intravenous oxytocin for the management of second-trimester pregnancies with intrauterine fetal death: a randomized clinical trial. *Journal of Obstetrics and Gynaecology Research* 2016;**42**(3):246-51.

Abeysundara 2012 *{published data only}*

Abeysundara ID, Herath RP, Wijesinghe PS. A qualitative study on patients' perceptions of expectant management of incomplete miscarriage. *BJOG: an international journal of obstetrics and gynaecology* 2012;**119**(Suppl 1):150.

Ajand 2017 *{published data only}*

Ajand M, IRCT201704179014N159. Comparison of the effect of vaginal versus sublingual misoprostol in medical induction of missed abortions: a randomized clinical trial. http://en.irct.ir/trial/9597 2017.

Al 2003 *{published data only}*

Al Inizi SA, Ezimokhai M. Vaginal misoprostol versus dinoprostone for the management of missed abortion. *International Journal of Gynecology & Obstetrics* 2003;**83**:73-4.

Al-Bdour 2007 *{published data only}*

Al-Bdour AN, Akasheh H, Al-Jayousi T. Missed abortion: termination using single-dose versus two doses of vaginal misoprostol tablets. *Pakistan Journal of Medical Sciences* 2007;**23**(6):920-3.

Ali 2015 *{published data only}*

Ali MK, NCT02573051. Misoprostol plus isosorbide mononitrate versus misoprostol for termination of anembryonic pregnancy. https://clinicaltrials.gov/ct2/show/NCT02573051 2015.

Ali 2017 *{published data only}*

Ali MK, NCT03148314. Home-based extended low dose buccal misoprostol versus hospital-based standard vaginal dose in management of first trimester missed abortion. https://clinicaltrials.gov/ct2/show/NCT03148314 (11 May 2017).

Allameh 2020 *{published data only}*

Allameh Z, Goharian M, Eslamian M. Effect of misoprostol with and without letrozole on induction of abortion for women with first-trimester missed abortion. *International Journal of Gynaecology and Obstetrics* 2020 Jul 22;**151**(2):214-8. [CENTRAL: CN-02137849] [EMBASE: 2006040208] [PMID: 32700359]

Almog 2005 *{published data only}*

Almog B, Levin I, Winkler N, Fainaru O, Pauzner D, Lessing JB, et al. The contribution of laminaria placement for cervical ripening in second trimester termination of pregnancy induced by intra-amniotic injection of prostaglandin F(2)alpha followed by concentrated oxytocin infusion. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2005;**118**:32-5.

Altaf 2006 *{published data only}*

Altaf F, Sultana N, Iqbal N. Therapeutic abortions; efficacy of intra-vaginal misoprostol in comparison to extra amniotically administered prostaglandin f2a. *Professional Medical Journal* 2006;**13**(3):417-22.

Ameen 2009 *{published data only}*

Ameen NS, NCT00892229. Buccal versus vaginal misoprostol for cervical ripening prior to surgical termination of the first trimester missed abortion in Erbil. https://clinicaltrials.gov/ct2/show/NCT00892229 2009.

Amjad 1999 *{published data only}*

Amjad T, Akhtar S. Termination of pregnancy with foetal death in second trimester: Foley's catheter versus extra amniotic prostaglandins. *Journal of the College of Physicians & Surgeons Pakistan* 1999;**9**:403-5.

Anderman 2000 *{published data only}*

Anderman S, Jaschevatzky OE, Ballas S. Comparison between a double balloon device and the Foley catheter in extraamniotic prostaglandin F2a infusion for termination of midtrimester missed abortion [abstract]. In: XVI FIGO World Congress of Obstetrics & Gynecology (Book 2); 2000 Sept 3-8; Washington DC, USA. 2000:161.

Anderson 2009 *{published data only}*

* Anderson J, Gouk E, Young L, Turnbull L, Sayeed G, Elattar A, et al. A randomised controlled trial of oral versus vaginal misoprostol for medical management of early fetal demise. *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S533.

Gouk E, ISRCTN85124072. Oral versus vaginal misoprostol for medical management of early foetal demise. http://www.isrctn.com/ISRCTN85124072 2009.

Aramide 2014 *{published data only}*

Aramide TM, Olusegun AK, Akinfolarin AC, Oriola DF. Oral misoprostol in the prevention of uterine bleeding after surgical

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

evacuation of first trimester abortion: a comparative study of three uterotonic agents. Nigerian Journal of Clinical Practice 2014 Jan-Feb;**17**(1):10-3. [CENTRAL: CN-00982541] [PMID: 24326799]

Arteaga-Troncoso 2005 *{published data only}*

Arteaga-Troncoso G, Villegas-Alvarado A, Belmont-Gomez A, Martinez-Herrera FJ, Villagrana-Zesati R, Guerra-Infante F. Intracervical application of the nitric oxide donor isosorbide dinitrate for induction of cervical ripening: a randomised controlled trial to determine clinical efficacy and safety prior to first trimester surgical evacuation of retained products of conception. *BJOG: an international journal of obstetrics and gynaecology* 2005;**112**(12):1615-9.

Autry 1999 *{published data only}*

Autry A, Jacobson G, Sandhu R, Isbill K. Medical management of non-viable early first trimester pregnancy. *International Journal of Gynecology & Obstetrics* 1999;**67**(1):9-13.

Avila-Vergara 1997 *{published data only}*

Avila-Vergara MA, Morgan-Ortiz F, Fragoza-Sosa O, Haro-Garcia L. [Cervical labor induction with prostaglandin E2 in patients with fetal death] [Maduracion cervical con prostaglandina E2 en pacientes con feto muerto]. *Ginecologia y Obstetricia de Mexico* 1997;**65**:155-8.

Avila VergaraMa 1997 *{published data only}*

Avila-Vergara Ma, Morgan-Ortiz F Fragoza-Sosa O Haro-Garcia L. [Cervical labor induction with prostaglandin E2 in patients with fetal death]. *Ginecologia y Obstetricia de Mexico* 1997;**65**:155-8.

Aye 2017 *{published data only}*

Aye TT, Aung KL, Myint SS. A comparative study on effect of sublingual versus vaginal misoprostol in management of first trimester miscarriage in Magway Teaching Hospital. *Journal of Obstetrics and Gynaecology Research* 2017;**43**:185-6, Abstract no: 9020 https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/jog.13396.

Ayudhaya 2006 *{published data only}*

Ayudhaya OP, Herabutya Y, Chanrachakul B, Ayuthaya NI, O-Prasertsawat P. A comparison of the efficacy of sublingual and oral misoprostol 400 microgram in the management of early pregnancy failure: a randomized controlled trial. *Journal of the Medical Association of Thailand* 2006;**89**(Suppl 4):S5-S10.

Azra 2007 *{published data only}*

Azra B, Shakeel S, Nilofer M. A comparison of two protocols of intra vaginal misoprostol for second trimester medical termination of pregnancy. *Pakistan Armed Forces Medical Journal* 2007;**57**(1):61-5.

Bagratee 2009 *{published data only}*

Bagratee J, Regan L, Khullar V, Moodley J, Connolly C. Does the volume of retained products of conception and hormonal parameters influence the success of conservative methods of management of first trimester miscarriage? *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S116.

Bani-Irshaid 2006 *{published data only}*

Bani-Irshaid I, Athamneh TZ, Bani-Khaled D, Al-Momani M, Dahamsheh H. Termination of second and early third trimester pregnancy: comparison of 3 methods. *Eastern Mediterranean Health Journal* 2006;**12**(5):605-9.

Barnhart 2004 *{published data only}*

Barnhart KT, Bader T, Huang X, Frederick MM, Timbers KA, Zhang JJ. Hormone pattern after misoprostol administration for a nonviable first-trimester gestation. *Fertility and Sterility* 2004;**81**(4):1099-105.

Bartz 2013 *{published data only}*

Bartz D, Maurer R, Allen RH, Fortin J, Kuang B, Goldberg AB. Buccal misoprostol compared with synthetic osmotic cervical dilator before surgical abortion: a randomized controlled trial. *Obstetrics and Gynecology* 2013;**122**(1):57-63.

Bebbington 2002 *{published data only}*

Bebbington MW, Kent N, Lim K, Gagnon A, Delisle MF, Tessier F, et al. A randomized controlled trial comparing two protocols for the use of misoprostol in midtrimester pregnancy termination. *American Journal of Obstetrics and Gynecology* 2002;**187**(4):853-7.

Behrashi 2008 *{published data only}*

* Behrashi M, Mahdian M. Vaginal versus oral misoprostol for second-trimester pregnancy termination: a randomized trial. *Pakistan Journal of Biological Sciences* 2008;**11**(21):2505-8.

Behrashi M. Comparison between the oral and vaginal misoprostol effects on pregnancy termination in second trimester. en.search.irct.ir/view/90 (first received 27 September 2008).

Ben-Meir 2009 *{published data only}*

Ben-Meir A, Erez Y, Feigenberg T, Hamani Y, Laufer N, Rojansky N. Mifepristone followed by high-dose oxytocin drip for second-trimester abortion: a randomized, double-blind, placebo-controlled, pilot study. *Journal of Reproductive Medicine* 2009;**54**(8):511-6.

Betstadt 2008 *{published data only}*

Betstadt S//NCT00468299. MiMi: a randomized trial of mifepristone and misoprostol for treatment of early pregnancy failure. clinicaltrials.gov/ct2/show/NCT00468299 (first received 1 May 2007).

* Betstadt S. MiMi: a randomized trial of mifepristone and misoprostol for treatment of early pregnancy failure. ClinicalTrials.gov (http://clinicaltrials.gov/) (accessed 20 February 2008) 2008.

Biswas 2007 *{published data only}*

Biswas SC, Dey R, Jana R, Chattopadhyay N. Comparative study of intravaginal misoprostol and extra amniotic ethacridine lactate instillation for mid trimester pregnancy termination. *Journal of Obstetrics and Gynaecology of India* 2007;**57**(3):211-3.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Blanchard 2004 *{published data only}*

Blanchard K, Taneepanichskul S, Kiriwat O, Sirimai K, Svirirojana N, Mavimbela N, et al. Two regimens of misoprostol for treatment of incomplete abortion. *Obstetrics & Gynecology* 2004;**103**(5 Pt 1):860-5.

Blohm 1997 *{published data only}*

Blohm F, Hahlin M, Nielsen S, Milsom I. Fertility after a randomised trial of spontaneous abortion managed by surgical evacuation or expectant treatment [letter]. *Lancet* 1997;**349**(9057):995.

Bracken 2014 *{published data only}*

Bracken H, Ngoc NT, Banks E, Blumenthal P, Derman R, Patel A, et al. Misoprostol for treatment of intrauterine fetal death at 14-28 weeks of pregnancy. *American Journal of Obstetrics and Gynecology* 2013;**208**(1 Suppl):S62-S63.

* Bracken H, Ngoc NT, Banks E, Blumenthal PD, Derman RJ, Patel A, et al. Buccal misoprostol for treatment of fetal death at 14-28 weeks of pregnancy: a double-blind randomized controlled trial. *Contraception* 2014;**89**(3):187-92.

Bracken 2019 *{published data only}*

Bracken H, Zuberi N, de Guevara Puerto AL, Mayi-Tsonga S, Buendia Gomez M, Irfan Ahmed S, et al. Mifepristone and sublingual misoprostol versus sublingual misoprostol alone for missed abortion: results of a randomized placebo-controlled trial. *Contraception* 2019 May;**99**(5):315-6. [CENTRAL: CN-01937106] [EMBASE: 2001888624]

Brouns 2010 *{published data only}*

Brouns JF, van Wely M, Burger MP, van Wijngaarden WJ. Comparison of two dose regimens of misoprostol for second-trimester pregnancy termination. *Contraception* 2010;**82**(3):266-75.

Cabrol 1990 *{published data only}*

Cabrol D, Dubois C, Cronje H, Gonnet JM, Guillot M, Maria B, et al. Induction of labor with mifepristone (RU 486) in intrauterine fetal death. *American Journal of Obstetrics and Gynecology* 1990;**163**:540-2.

Caliskan 2005 *{published data only}*

Caliskan E, Dilbaz S, Doger E, Ozeren S, Dilbaz B. Randomized comparison of 3 misoprostol protocols for abortion induction at 13-20 weeks of gestation. *Journal of Reproductive Medicine* 2005;**50**(3):173-80.

Caliskan 2009 *{published data only}*

Caliskan E, Doger E, Cakiroglu Y, Corakci A, Yucesoy I. Sublingual misoprostol 100 microgram versus 200 microgram for second trimester abortion: a randomised trial. *European Journal of Contraception & Reproductive Health Care* 2009;**14**(1):55-60.

Chen 2008a *{published data only}*

Chen FC, Bergann A, Krosse J, Merholz A, David M. Isosorbide mononitrate vaginal gel versus misoprostol vaginal gel versus Dilapan-S for cervical ripening before first trimester curettage. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2008;**138**(2):176-9.

Chittacharoen 2003 *{published data only}*

Chittacharoen A, Herabutya Y, Punyavachira P. A randomized trial of oral and vaginal misoprostol to manage delivery in cases of fetal death. *Obstetrics & Gynecology* 2003;**101**:70-3.

Chowdhury 2012 *{published data only}*

Chowdhury S, Uddin AW. Misoprostol in the management of second trimester missed abortion: a randomized controlled trial. *International Journal of Gynaecology and Obstetrics* 2012;**119**(Suppl 3):S310.

Cleeve 2016 *{published data only}*

Cleeve A, Byamugisha J, Gemzell-Danielsson K, Mbona Tumwesigye N, Atuhairwe S, Faxelid E, et al. Women's acceptability of misoprostol treatment for incomplete abortion by midwives and physicians - a randomized controlled equivalence trial at district level, Uganda. *International Journal of Gynecology and Obstetrics* 2015;**131**(Suppl 5):E295.

* Cleeve A, Byamugisha J, Gemzell-Danielsson K, Tumwesigye NM, Atuhairwe S, Faxelid E, et al. Women's acceptability of misoprostol treatment for incomplete abortion by midwives and physicians - Secondary outcome analysis from a randomized controlled equivalence trial at district level in Uganda. *PloS One* 2016;**11**(2):e0149172.

Clevin 2001 *{published data only}*

Clevin L, Munk T, Hansen TR. Spontaneous abortion. Drug treatment versus surgery [Spontan abort. Medicinsk versus kirurgisk behandling]. *Ugeskrift for Laeger* 2001;**163**(15):2136-9.

Creinin 1997 *{published data only}*

Creinin MD, Moyer R, Guido R. Misoprostol for medical evacuation of early pregnancy failure. *Obstetrics & Gynecology* 1997;**89**:768-72.

Creinin 2004 *{published data only}*

Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J, NICHD Management of Early Pregnancy Failure Trial. Endometrial thickness after misoprostol use for early pregnancy failure. *International Journal of Gynaecology & Obstetrics* 2004;**86**(1):22-6.

Cruz 2017 *{published data only}*

Cruz RP, Scheffler MH, da Silva DM, Guedes Neto EP, Savaris RF. Moistening the new vaginal misoprostol tablets: does it increase the efficacy of cervical priming before manual vacuum aspiration in first-trimester miscarriage? A randomised clinical trial. *European Journal of Contraception & Reproductive Health Care* 2017;**22**(6):407-11.

Danielsson 2012 *{published data only}*

Danielsson KG, NCT01615224. Repeated doses of misoprostol for treatment of missed abortion. https://clinicaltrials.gov/ct2/show/NCT01615224 2012.

David 2003 *{published data only}*

David M, Chen FC, Lichtenegger W. NO-donor nitroglycerin versus the prostaglandin gemeprost for cervical ripening in first trimester missed abortion. *International Journal of Gynecology & Obstetrics* 2003;**83**:71-2.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

David 2005 *{published data only}*

David M, Chen FC. Comparison of isosorbide mononitrate (Mono Mack) and misoprostol (Cytotec) for cervical ripening in the first trimester missed abortion. *Archives of Gynecology and Obstetrics* 2005;**273**(3):144-5.

Davis 2004 *{published data only}*

Davis AR, Robilotto CM, Westhoff CL, Forman S, Zhang J, NICHD MofEPFT. Bleeding patterns after vaginal misoprostol for treatment of early pregnancy failure. *Human Reproduction* 2004;**19**(7):1655-8.

Dee 2009 *{published data only}*

Dee MT, Dancel MA. A prospective randomized study comparing the use of intrauterine to vaginal misoprostol for pre-curettage cervical priming of early pregnancy failure. *Philippine Journal of Obstetrics & Gynecology* 2009;**33**(3):83.

Dehbashi 2016 *{published data only}*

Dehbashi Z, Moosazadeh M, Afshari M. Comparison between sublingual and vaginal route of misoprostol in management of first trimester miscarriage missing. *Materia Socio-Medica* 2016;**28**(4):271-3.

Devall 2019 *{published data only}*

Devall A, ISRCTN15586426. A pilot trial to evaluate the benefit of using ultrasound during surgical management of miscarriage. http://www.isrctn.com/ISRCTN15586426 2019.

Dhillon 2015 *{published data only}*

Dhillon AP, Shergill HK, Yadav P. Comparative study between vaginal isosorbide mononitrate and misoprostol for induction of cervical ripening prior to surgical evacuation of first trimester embryonic demise. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology* 2015;**4**(2):398-401.

Dickinson 1998 *{published data only}*

Dickinson JE, Godfrey M, Evans SF. Efficacy of intravaginal misoprostol in second-trimester pregnancy termination: a randomized controlled trial. *Journal of Maternal-Fetal Medicine* 1998;**7**:115-9.

Dickinson 2002 *{published data only}*

Dickinson JE, Evans SF. The optimization of intravaginal misoprostol dosing schedules in second-trimester pregnancy termination. *American Journal of Obstetrics and Gynecology* 2002;**186**(3):470-4.

Dickinson 2003 *{published data only}*

Dickinson JE, Evans SF. A comparison of oral misoprostol with vaginal misoprostol administration in second-trimester pregnancy termination for fetal abnormality. *Obstetrics & Gynecology* 2003;**101**:1294-9.

Diop 2009 *{published data only}*

Diop A, Raghavan S, Rakotovao JP, Comendant R, Blumenthal PD, Winikoff B. Two routes of administration for misoprostol in the treatment of incomplete abortion: a randomized clinical trial. *Contraception* 2009;**79**(6):456-62.

Dunford 2012 *{published data only}*

Dunford A, ACTRN12612001254886. Among women with first trimester miscarriage, is the combination of mifepristone plus misoprostol superior to misoprostol alone for reducing the need for surgical uterine evacuation and repeat doses of misoprostol? https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12612001254886 2012.

Dunn 2008 *{published data only}*

Dunn TS, Gregory N, Parrish A, Coddington CC III. Oral misoprostol compared with laminaria before dilation and curettage for missed abortion. *Obstetrics & Gynecology* 2008;**111**(4 Suppl):23S.

Egarter 1995 *{published data only}*

Egarter C, Lederhilger J, Kurz C, Karas H, Reisenberger K. Gemeprost for first trimester missed abortion. *Archives of Gynecology & Obstetrics* 1995;**256**(1):29-32.

Elami-Suzin 2013 *{published data only}*

Elami-Suzin M, Freeman MD, Porat N, Rojansky N, Laufer N, Ben-Meir A. Mifepristone followed by misoprostol or oxytocin for second-trimester abortion: a randomized controlled trial. *Obstetrics and Gynecology* 2013;**122**(4):815-20.

Elbareg 2018 *{published data only}*

Elbareg A, Essadi FM. Letrozole combined with misoprostol versus (miso) alone in management of delayed miscarriages. *International Journal of Gynecology and Obstetrics* 2018;**143**(S3):387.

Elhassan 2008 *{published data only}*

Elhassan EM, Abubaker MS, Adam I. Sublingual compared with oral and vaginal misoprostol for termination of pregnancy with second-trimester fetal demise. *International Journal of Gynecology & Obstetrics* 2008;**100**(1):82-3.

El Sokkary 2016 *{published data only}*

El Sokkary HHA. Comparison between sublingual and vaginal administration of misoprostol in management of missed abortion. *Journal of Obstetrics and Gynaecology of India* 2016;**66**(S1):S24-9.

Eng 1997 *{published data only}*

Eng NS, Guan AC. Comparative study of intravaginal misoprostol with gemeprost as an abortifacient in second trimester missed abortion. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1997;**37**(3):331-4.

Eppel 2005 *{published data only}*

Eppel W, Facchinetti F, Schleussner E, Piccinini F, Pizzi C, Gruber DM, et al. Second trimester abortion using isosorbide mononitrate in addition to gemeprost compared with gemeprost alone: a double-blind randomized, placebo-controlled multicenter trial. *American Journal of Obstetrics and Gynecology* 2005;**192**:856-61.

Eslamian 2007 *{published data only}*

Eslamian L, Gosili R, Jamal A, Alyassin A. A prospective randomized controlled trial of two regimens of vaginal

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

misoprostol in second trimester termination of pregnancy. *Acta Medica Iranica* 2007;**45**(6):497-500.

EUCTR2011-001505-26-SE *{published data only}*

EUCTR2011-001505-26-SE. Repeated doses of misoprostol for medical treatment of intact miscarriage. Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2011-001505-26-se 2011.

EUCTR2011-001505-26-SE. Repeated doses of misoprostol for medical treatment of missed abortion. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-001505-26 2011.

Ezzatosadat 2012 *{published data only}*

Ezzatosadat HJ, IRCT201207259491N3. The effect of adding hyoscine to vaginal misoprostol on shortening the induction time of abortion. http://en.irct.ir/trial/10080 2012.

Facchinetti 2001 *{published data only}*

Facchinetti F, Piccinini F, Fazzio M, Volpe A. Safety and efficacy of nitroprusside gel for cervical ripening [abstract]. *American Journal of Obstetrics and Gynecology* 2001;**185**(6 Suppl):S107.

Fadalla 2004 *{published data only}*

Fadalla F, Mirghani OA, Adam I. Oral misoprostol vs. vaginal misoprostol for termination of pregnancy with intrauterine fetal demise in the second-trimester. *International Journal of Gynecology & Obstetrics* 2004;**86**:52-3.

Farooq 2018 *{published data only}*

Farooq F, Javed L, Mumtaz A, Naveed N. Comparison of manual vacuum aspiration, and dilatation and curettage in the treatment of early pregnancy failure. *Journal of Ayub Medical College, Abbottabad : JAMC* 2011;**23**(3):28-31.

* Farooq F. Comparison of manual vacuum aspiration and dilatation and curettage in the treatment of early pregnancy failure. *International Journal of Gynecology and Obstetrics* 2018;**143**(S3):363-4.

Faxelid 2012 *{published data only}*

Faxelid E, NCT01743508. Misoprostol treatment of incomplete abortion by midwives and physicians. A randomized control trial in Uganda. https://clinicaltrials.gov/ct2/show/NCT01743508 2012.

Feldman 2003 *{published data only}*

Feldman DM, Borgida AF, Rodis JF, Leo MV, Campbell WA. A randomized comparison of two regimens of misoprostol for second-trimester pregnancy termination. *American Journal of Obstetrics and Gynecology* 2003;**189**:710-3.

Fiala 2005 *{published data only}*

Fiala C, Swahn ML, Stephansson O, Gemzell-Danielsson K. The effect of non-steroidal anti-inflammatory drugs on medical abortion with mifepristone and misoprostol at 13-22 weeks gestation. *Human Reproduction* 2005;**20**(11):3072-7.

Firouzabadi 2012 *{published data only}*

Firouzabadi RD, Sekhavat L, Tabatabaii A, Hamadani S. Laminaria tent versus misoprostol for cervical ripening before surgical process in missed abortion. *Archives of Gynecology and Obstetrics* 2012;**285**(3):699-703.

Freeman 2016 *{published data only}*

Freeman MD, Porat N, Rojansky N, Elami-Suzin M, Winograd O, Ben-Meir A. Physical symptoms and emotional responses among women undergoing induced abortion protocols during the second trimester. *International Journal of Gynaecology and Obstetrics* 2016;**135**(2):154-7.

Ghorab 1998 *{published data only}*

Ghorab MN, El Helw BA. Second-trimester termination of pregnancy by extra-amniotic prostaglandin F2alpha or endocervical misoprostol A comparative study. *Acta Obstetricia et Gynecologica Scandinavica* 1998;**77**:429-32.

Gilles 2004 *{published data only}*

Gilles J, Creinin MM, Barnhart KT, Westhoff C, Frederick MM, Zang J. Wet versus dry intravaginal misoprostol application for treatment of early pregnancy failure [abstract]. *Fertility and Sterility* 2002;**78**(3 Suppl 1):S64-5.

* Gilles JM, Creinin MD, Barnhart K, Westhoff C, Frederick MM, Zhang J. A randomized trial of saline solution-moistened misoprostol versus dry misoprostol for first-trimester pregnancy failure. *American Journal of Obstetrics and Gynecology* 2004;**190**:389-94.

Gonzalez 2001 *{published data only}*

Gonzalez JA, Carlan SJ, Alverson MW. Outpatient second trimester pregnancy termination. *Contraception* 2001;**63**(2):89-93.

Graziosi 2005 *{published data only}*

Graziosi G, Bruinse HW, Reuwer PJ, Teteringen O, Mol BJ. Fertility outcome after a randomized trial comparing curettage with misoprostol for treatment of early pregnancy failure. *Human Reproduction* 2005;**20**:1749-50.

Grimes 2005 *{published data only}*

Grimes DA, Smith MS, Witham AD. Mifepristone and misoprostol versus dilation and evacuation for midtrimester abortion: a pilot randomised controlled trial. *BJOG: an international journal of obstetrics and gynaecology* 2005;**111**:148-53.

Gronlund 2002 *{published data only}*

Gronlund A, Gronlund L, Clevin L, Andersen B, Palmgren N, Lidegaard O. Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation. A multi-center trial in Copenhagen county, Denmark. *Acta Obstetricia et Gynecologica Scandinavica* 2002;**81**:1060-5.

Guix 2005 *{published data only}*

Guix C, Palacio M, Figueras F, Bennasar M, Zamora L, Coll O, et al. Efficacy of two regimens of misoprostol for early second-trimester pregnancy termination. *Fetal Diagnosis and Therapy* 2005;**20**(6):544-8.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Halimi 2004 *{published data only}*

Halimi M. Therapeutic termination of second trimester pregnancy: a comparison of extra-amniotic Foley's catheter balloon alone with the combined use of Foley`s catheter balloon and extra-amniotic instillation of prostaglandin f2-alpha. *Journal of Postgraduate Medical Institute* 2004;**18**(3):408-18.

Harrington 2004 *{published data only}*

Harrington K, ISRCTN14476388. Out-patient management of missed miscarriage: a randomised trial of medical vs medical/ minimally invasive management using transcervical amnion rupture. http://www.isrctn.com/ISRCTN14476388 2004.

Hassan 2007 *{published data only}*

Hassan FI, Mostapha MK, Sattar MA, Marouf E, Azim SA. Oral versus rectal route of misoprostol administration: a randomized controlled trial. *Middle East Fertility Society Journal* 2007;**12**(1):53-6.

Hausler 1997 *{published data only}*

Hausler MC, Koroschetz F, Tamussino K, Walcher W. Is a curettage after spontaneous abortion still relevant? [Ist eine currettage nach abortus completus noch zeitgemals?]. *Geburtshilfe und Frauenheilkunde* 1997;**57**:396-9.

Heard 2002 *{published data only}*

Heard MJ, Stewart GM, Buster JE, Carson SA, Miller HJ. Outpatient management of missed abortion with vaginal misoprostol [abstract]. *Obstetrics & Gynecology* 2002;**99**(4 Suppl):20S.

Henshaw 1995 *{published data only}*

Henshaw RC, Hinshaw K, Smith NC, Templeton AA. The medical management of miscarriage. In: Fertility Society of Australia /Australasian Gynaecological Endoscopy Society; 1995 November 19-25; Melbourne, Australia. 1995:FSA75.

Herabutya 1997 *{published data only}*

Herabutya Y, O-Prasertsawat P. A comparison of intravaginal misoprostol with intracervical prostaglandin E2 gel for the management of dead fetus in utero. *Thai Journal of Obstetrics and Gynaecology* 1997;**9**(2):95-8.

Herabutya 1997a *{published data only}*

Herabutya Y, O-Prasertsawat P. Misoprostol in the management of missed abortion. *International Journal of Gynecology & Obstetrics* 1997;**56**(3):263-6.

Herabutya 2005 *{published data only}*

Herabutya Y, Chanrachakul B, Punyavachira P. A randomised controlled trial of 6 and 12 hourly administration of vaginal misoprostol for second trimester pregnancy termination. *BJOG: an international journal of obstetrics and gynaecology* 2005;**112**(9):1297-301.

Herman 2017 *{published data only}*

Herman HG, Kerner R, Gluck O, Feit H, Keidar R, Bar J, et al. Different routes of misoprostol for cervical priming in first trimester surgical abortions: a randomized blind trial. *Archives of Gynecology and Obstetrics* 2017;**295**:943-50.

Hernandez-Valencia 2003 *{published data only}*

Hernandez-Valencia M. Cervical ripening with prostaglandin E1: how an ambulatory method decreases the hospital stay in abortus with intrauterine fetal demise. *Fetal Diagnosis & Therapy* 2003;**18**:54-8.

Hidalgo 2010 *{published data only}*

Hidalgo M, Guerra M, Reyna E, Santos J, Mejia J, Reyna N, et al. [Isosorbide mononitrate or misoprostol for cervical ripening in missed pregnancies during first trimester] [Mononitrato de isosorbide o misoprostol en maduracion cervical en embarazos interrumpidos durante el primer trimestre]. *Clinica e Investigacion en Ginecologia y Obstetricia* 2010;**37**(6):218-22.

Hidar 2001 *{published data only}*

Hidar S, Fekih M, Chaieb A, Bibi M, Mellouli R, Khairi H. Oxytocin and misoprostol administered intravaginally for termination of pregnancy at 13 to 29 weeks of amenorrhoea. A prospective randomized trial [Apport de l'association d'ocytocine au misoprostol administre en intravaginal au cours des interruptions de grossesses entre 13 et 29 semaines d'amenorrhee. Essai clinique prospectif randomise.]. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* 2001;**30**(5):439-43.

Hidar 2005 *{published data only}*

Hidar S, Bouddebous M, Chaieb A, Jerbi M, Bibi M, Khairi H. Randomized controlled trial of vaginal misoprostol versus vaginal misoprostol and isosorbide dinitrate for termination of pregnancy at 13-29 weeks. *Archives of Gynecology and Obstetrics* 2005;**273**(3):157-60.

Hill 1991 *{published data only}*

Hill NC, Selinger M, Ferguson J, MacKenzie IZ. Management of intra-uterine fetal death with vaginal administration of gemeprost or prostaglandin E2: a random allocation controlled trial. *Journal of Obstetrics and Gynaecology* 1991;**11**:422-6.

Hinshaw 1995 *{published data only}*

Hinshaw HK. Medical management of miscarriage. In: Grundzinkas JG, editors(s). Problems in Early Pregnancy - Advances in Diagnosis and Management. London: RCOG, 1997.

* Hinshaw K, Rispin R, Henshaw R, Smith N, Templeton A. Medical versus surgical uterine evacuation in first trimester miscarriage: a prospective, pragmatic randomised trial. In: 27th British Congress of Obstetrics and Gynaecology; 1995 July 4-7; Dublin, Ireland. 1995:Abstract no: 4.

Hinshaw K, Rispin R, Smith N, Templeton A. Medical vs surgical management in first trimester miscarriage: a prospective, pragmatic random allocation trial. *Journal of Obstetrics and Gynaecology* 1993;**13**(5):404-5.

Rispin R, Hinshaw K, Henshaw R, Smith N, Templeton A. New aspects of care in the management of miscarriage. In: Proceedings of Research in Midwifery Conference; 1993 Sept 14; Birmingham, UK. 1993.

Hogg 2000 *{published data only}*

Hogg B, Owen J. Laminaria versus extraamniotic saline infusion (EASI) for cervical ripening and mid-trimester labor induction

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[abstract]. *American Journal of Obstetrics and Gynecology* 2000;**182**(1 Pt 2):S135.

Hombalegowda 2015 *{published data only}*

Hombalegowda RB, Samapthkumar S, Vana H, Jogi P, Ramaiah R. A randomized controlled trial comparing different doses of intravaginal misoprostol for early pregnancy failure. *Contraception* 2015;**92**(4):364-5.

Hooker 2016 *{published data only}*

* Hooker A, de Leeuw R, Thurkow A, Brolmann H, Huirne J. Prevention of adhesions post (spontaneous) abortion (PAPA study); a randomized controlled trial evaluating application of hyaluronic acid (HA). *Human Reproduction* 2016;**31**:i30-1.

Hooker A, Leeuw de R, Brolmann H, Huirne J. Does application of auto-cross linker hyaluronic acid in women following d&c for miscarriage with at least one d&c in history improve reproductive outcome? *Human Reproduction* 2017;**32**:i135.

Hooker A. Prevention of adhesions post (spontaneous) abortion (PPAPA study); a randomised controlled trial evaluating hyaluronic acid. *Gynecological Surgery* 2015;**12**(Suppl 1):S461, Abstract no: ES24-0434.

Hooker AB, de Leeuw R, van de Ven PM, Bakkum EA, Thurkow AL, Vogel NE, et al. Prevalence of intrauterine adhesions after the application of hyaluronic acid gel after dilatation and curettage in women with at least one previous curettage: Short-term outcomes of a multicenter, prospective randomized controlled trial. *Fertility and Sterility* 2017;**107**(5):1223–31.

Huchon 2015 *{published data only}*

Huchon C, Koskas M, Agostini A, Akladios C, Alouini S, Bauville E, et al. Operative hysteroscopy versus vacuum aspiration for incomplete spontaneous abortion (HY-PER): study protocol for a randomized controlled trial. *Trials* 2015;**16**(1):363.

Hughes 1996 *{published data only}*

Hughes J, Ryan M, Hinshaw K, Henshaw R, Rispin R, Templeton A. The costs of treating miscarriage: a comparison of medical and surgical management. *British Journal of Obstetrics and Gynaecology* 1996;**103**(12):1217-21.

Ibrahim 2019 *{published data only}*

Ibrahim HN, Mustafa ZM, Rajab HK. Comparison between the effectiveness of combination of letrozole with misoprostol and tamoxifen with misoprostol in medical termination of first trimester missed miscarriage. Indian Journal of Public Health Research and Development (first received 2019);**10**(8):2322-7. [CENTRAL: CN-01997127] [EMBASE: 2002799712]

Imran 2010 *{published data only}*

Imran F, Anser A, Danish N, Fatima N. Misoprostol for the purpose of mid-trimester termination of pregnancy: a comparative study with prostaglandin F2 alpha. *Journal of Ayub Medical College, Abbottabad: JAMC* 2010;**22**(4):87-91.

IRCT2015112421506N3 2016 *{published data only}*

IRCT2015112421506N3. INH plus misoprostol vs. misoprostol alone for early medical abortion: clinical trial. http://en.irct.ir/trial/18840 2016.

IRCT2016122729062N1 2016 *{published data only}*

IRCT2016122729062N1. Analyze the effect of the sesamum indicum on the termination of an incomplete abortion. http://en.irct.ir/trial/23446 2016.

Islam 2006 *{published data only}*

Islam A, Abbasi AN, Sarwar I. Use of Foley's catheter and prostaglandin F-2 alpha in second trimester termination of pregnancy. *Journal of Ayub Medical College, Abbottabad* 2006;**18**(3):35-9.

Jabir 2009a *{published data only}*

Jabir M, Smeet R. Comparison of oral and vaginal misoprostol for cervical ripening before evacuation of first trimester missed miscarriage. *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S209.

* Jabir M, Smeet RI. Comparison of oral and vaginal misoprostol for cervical ripening before evacuation of first trimester missed miscarriage. *Saudi Medical Journal* 2009;**30**(1):82-7.

Jain 1994 *{published data only}*

Jain JK, Mishell DR. A comparison of intravaginal misoprostol with prostaglandin E2 for termination of second-trimester pregnancy. [comment]. *New England Journal of Medicine* 1994;**331**:290-3.

Jain 1996 *{published data only}*

Jain JK, Mishell DR. A comparison of misoprostol with and without laminaria tents for induction of second-trimester abortion. *American Journal of Obstetrics and Gynecology* 1996;**175**:173-7.

Jain 1999 *{published data only}*

Jain JK, Mishell DR. A comparison of two dosing regimens of intravaginal misoprostol for second-trimester pregnancy termination. *Obstetrics & Gynecology* 1999;**93**:571-5.

Jamilian 2014 *{published data only}*

Jamilian M, IRCT201403244686N11. The comparison of the efficacy of oral castor oil with vaginally misoprostol and vaginally misoprostol alone in the treatment of missed abortion. http://en.irct.ir/trial/5024 2014.

Javadi 2015 *{published data only}*

Javadi E, IRCT2015050119037N8. Comparison the effect of letrozole plus misoprostol with misoprostol alone on induction of first trimester abortion in pregnant women. http://en.irct.ir/trial/17132 2015.

Johnson 1997 *{published data only}*

Johnson N, Priestnall M, Marsay T, Ballard P, Watters J. A randomised trial evaluating pain and bleeding after a first trimester miscarriage treated surgically or medically. *European*

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Journal of Obstetrics & Gynecology and Reproductive Biology 1997;**72**(2):213-5.

Kakinuma 2020 *{published data only}*

Kakinuma T, Kakinuma K, Sakamoto Y, Kawarai Y, Saito K, Ihara M, et al. Safety and efficacy of manual vacuum suction compared with conventional dilatation and sharp curettage and electric vacuum aspiration in surgical treatment of miscarriage: a randomized controlled trial. *BMC Pregnancy and Childbirth* 2020;**20**(1):695. [CENTRAL: CN-02200866] [EMBASE: 2007309665] [PMID: 33198679]

Kamal 2005 *{published data only}*

Kamal R, Parveeen F, Mazhar SB. Role of misoprostol in vaginal versus double oro-vaginal route for termination of pregnancy in mid trimester pregnancy. *Annals of Pakistan Institute of Medical Sciences* 2005;**1**(4):196-200.

Kanhai 1988 *{published data only}*

Kanhai HH, Keirse MJ. Intravenous administration of sulfprostone for the induction of labour after fetal death: a randomized comparison of two dose schedules. In: 12th FIGO World Congress of Gynecology and Obstetrics; 1988 October 23-28; Brazil. 1988:201-2.

Kanhai HH, Keirse MJ. Intravenous administration of sulprostone for the induction of labour after fetal death: a randomized comparison of two dose schedules. In: Proceedings of 1st European Congress on Prostaglandins in Reproduction; 1988 July 6-9; Vienna, Austria. 1988:45.

Kanhai 1989 *{published data only}*

Kanhai HH, Keirse MJ. Induction of labour after fetal death: a randomized controlled trial of two prostaglandin regimens. *British Journal of Obstetrics and Gynaecology* 1989;**96**:1400-4.

Kapp 2007 *{published data only}*

Kapp N, Todd CS, Yadgarova KT, Alibayeva G, Nazarova D, Loza O, et al. A randomized comparison of misoprostol to intrauterine instillation of hypertonic saline plus a prostaglandin F2alpha analogue for second-trimester induction termination in Uzbekistan. *Contraception* 2007;**76**(6):461-6.

Kara 1999 *{published data only}*

Kara M, Ozden S, Eroglu M, Cetin A, Arioglu P. Comparison of misoprostol and dinoproston administration for the induction of labour in second trimester pregnancies in cases of intrauterine fetal loss. *Italian Journal of Gynaecology & Obstetrics* 1999;**11**:13-6.

Khanam 2019 *{published data only}*

Khanam S, Meraj B, Dawood NS, Asif U. An experience of vaginal misoprostol versus sublingual use in cervical ripening before surgical evacuation. *PakistanJournal of Medical and Health Sciences* 2019;**13**(3):769-71.

Khoosideh 2017 *{published data only}*

Khoosideh M, Yarmohammadi N, Shahriari A, Sheikh M. Sublingual misoprostol plus laminaria for cervical preparation before surgical management of late first trimester missed abortions, a randomized controlled trial. *Journal of Maternal-Fetal & Neonatal Medicine* 2017;**30**(3):317-22.

Khosravi 2017 *{published data only}*

Khosravi D, IRCT2017040633255N1. Comparison of the effect between two dose (800 µg/day & 400 µg/6) of vaginal misoprostol in the termination of first-trimester pregnancy: a double-blinded randomized trial. https://en.irct.ir/trial/25706 (25 June 2017).

Klingberg-Allvin 2015 *{published data only}*

Klingberg-Allvin M, Cleeve A, Atuhairwe S, Tumwesigye NM, Faxelid E, Byamugisha J, et al. Comparison of treatment of incomplete abortion with misoprostol by physicians and midwives at district level in Uganda: a randomised controlled equivalence trial. *Lancet* 2015;**385**(9985):2392-8.

Klingberg-Alvin M, Cleeve A, Atuhairwe S, Mbona Tumwesigye N, Faxelid E, Byamugisha J, et al. Comparison of treatment of incomplete abortion with misoprostol by physicians and midwives at district level in Uganda: a randomised controlled equivalence trial. *International Journal of Gynecology and Obstetrics* 2015;**131**(Suppl 5):E86.

Kovavisarach 2005 *{published data only}*

Kovavisarach E, Jamnansiri C. Intravaginal misoprostol 600ug and 800ug for the treatment of early pregnancy failure. *International Journal of Gynecology & Obstetrics* 2005;**90**(3):208-12.

Kurshid 2010 *{published data only}*

Kurshid R, Ahmed A, Mir S, Ul Shamas I. To assess the efficacy of two regimens of misoprostol for second trimester pregnancy termination-a randomized comparison. *Internet Journal of Gynecology and Obstetrics* 2010;**14**(1):No pagination.

Kushwah 2009 *{published data only}*

* Kushwah B, Singh A. Sublingual versus oral misoprostol for uterine evacuation following early pregnancy failure. *International Journal of Gynecology & Obstetrics* 2009;**106**(1):43-5.

Kushwah DS, Kushwah B, Salman MT, Verma VK. Acceptability and safety profile of oral and sublingual misoprostol for uterine evacuation following early fetal demise. *Indian Journal of Pharmacology* 2011;**43**(3):306-10.

Lei 2015 *{published data only}*

Lei Y, ChiCTR-IOR-15007664. Comparion of the treatment efficacy for between combination drug mifepristone and misoprostol abortion and B ultrasound-guided curettage. http://www.chictr.org.cn/showproj.aspx?proj=12889 2015.

Lelaidier 1993 *{published data only}*

Lelaidier C, Baton-Saint-Mleux C, Fernandez H, Bourget P, Frydman R. Mifepristone (RU486) induces embryo expulsion in first trimester non-developing pregnancies: a prospective randomized trial. *Human Reproduction* 1993;**8**(3):492-5.

Lemmers 2016 *{published data only}*

Lemmers M, Verschoor MA, Bossuyt PM, Huirne JA, Spinder T, Nieboer TE, et al. Cost- effectiveness of curettage versus

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

expectant management in women with an incomplete evacuation after misoprostol treatment for first trimester miscarriage: a randomized controlled trial and cohort study. *Acta Obstetricia Et Gynecologica Scandinavica* 2018;**97**(3):294-300.

* Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Opmeer BC, Bossuyt PM, et al. Misorest: surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: a randomized controlled trial. *Human Reproduction* 2016;**31**(11):2421-7.

Lemmers M, Verschoor MA, Overwater K, Bossuyt PM, Hendriks D, Hemelaar M, et al. Fertility and obstetric outcomes after curettage versus expectant management in randomised and non-randomised women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2017;**211**:78-82.

Verschoor MA, Lemmers M, Bossuyt PM, Graziosi GC, Hajenius PJ, Hendriks DJ, et al. Surgical versus expectant management in women with an incomplete evacuation of the uterus after treatment with misoprostol for miscarriage: the MisoREST trial. *BMC Pregnancy and Childbirth* 2013;**13**:102.

Verschoor MA, NTR3310. MisoREST: A multicenter randomized controlled trial comparing curettage and expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage. https://www.trialregister.nl/trial/3166 2012.

Leung 2004 *{published data only}*

Leung SW, Pang MW, Chung TK. Retained products of gestation in miscarriage: an evaluation of transvaginal ultrasound criteria for diagnosing an "empty uterus". *American Journal of Obstetrics and Gynecology* 2004;**191**:1133-7.

Li 2018 *{published data only}*

Li X, Wu L, Zhou Y, Fan X, Huang J, Wu J, et al. New crosslinked hyaluronan gel for the prevention of intrauterine adhesions after dilation and curettage in patients with delayed miscarriage: a prospective, multicenter, randomized, controlled trial. *Journal of Minimally Invasive Gynecology* 2018;**26**(1):94-9.

Linn 2015 *{published data only}*

Linn TW, Nyunt KK, Ku SK. Effectiveness of low doses vaginal misoprostol in intrauterine fetal death. *Journal of Obstetrics and Gynaecology Research* 2015;**41**(Suppl S1):60, Abstract no: FC 10.12.

Lippert 1978 *{published data only}*

Lippert TH, Luthi A. Induction of labour with prostaglandin E2 gel in cases of intrauterine fetal death. *Prostaglandins* 1978;**15**:533-42.

Louey 2000 *{published data only}*

Louey K. Misoprostol for the medical management of miscarriage [ongoing trial]. Personal communication 2000.

Lu 2014 *{published data only}*

Lu PH, Lu J, Zou S. Comparisons of the effects of misoprostol by two different application on the treatment of missed abortion. *Chinese Journal of Pharmaceutical Biotechnology* 2014;**21**(2):159-61.

Lughmani 2007 *{published data only}*

Lughmani ST. A comparison of intravaginal misoprostol with prostaglandin E2 for termination of 1st trimester pregnancy. *BJOG: an international journal of obstetrics and gynaecology* 2008;**115**(s1):179.

* Lughmani ST. A comparison of intravaginal misoprostol with prostaglandin E2 for termination of 1st trimester pregnancy. Double blind randomized trial [abstract]. In: 31st British International Congress of Obstetrics and Gynaecology; 2007 July 4-6; London, UK. 2007:209.

Mahjabeen, 2009 *{published data only}*

Mahjabeen, Khawaja NP, Rehman R. Comparison of oral versus vaginal misoprostol for mid-trimester pregnancy termination. *Journal of the College of Physicians & Surgeons Pakistan* 2009;**19**(6):359-62.

Makenzius 2017 *{published data only}*

* Makenzius M, Oguttu M, Klingberg-Allvin M, Gemzell-Danielsson K, Odero TM, Faxelid E. Post-abortion care with misoprostol - equally effective, safe and accepted when administered by midwives compared to physicians: a randomised controlled equivalence trial in a low-resource setting in Kenya. *BMJ Open* 2017;**7**(10):e016157.

Makenzius M, Oguttu MA, Odera T, Klingberg-Allvin M, Gemzell-Danielsson K, Faxelid E. Post-abortion care (PAC) and contraceptive counselling by midwives or physicians: a facility based study in Kisumu, Western Kenya. In: 31st International Confederation of Midwives Triennial Congress. Midwives - Making a Difference in the World; 2017 June 18-22; Toronto, Canada. 2017:Abstract no: F14.01.

Makhlouf 2003 *{published data only}*

Makhlouf AM, Al-Hussaini TK, Habib DM, Makarem MH. Second-trimester pregnancy termination: comparison of three different methods. *Journal of Obstetrics and Gynaecology* 2003;**23**:407-11.

Marfou 2012 *{published data only}*

Marfou J, Shahbazian N, Abdollahi M. Comparison of effect of oxytocin and prostaglandin E1 on cervix prior to curettage in first trimester. *Iranian Journal of Obstetrics, Gynecology and Infertility* 2012;**15**(28):9-12.

Martin 1955 *{published data only}*

Martin RH, Menzies DN. Oestrogen therapy in missed abortion and labour. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1955;**62**:256-8.

Marwah 2016 *{published data only}*

Marwah S, Gupta S, Batra NP, Bhasin V, Sarna V, Kaur N. A comparative study to evaluate the efficacy of vaginal vs oral prostaglandin E1 analogue (misoprostol) in management of first

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

trimester missed abortion. *Journal of Clinical and Diagnostic Research* 2016;**10**(5):QC14-8.

Mitwaly 2016 *{published data only}*

Mitwaly AB, Abbas AM, Abdellah MS. Intra uterine extra-amniotic versus vaginal misoprostol for termination of second trimester miscarriage: a randomized controlled trial. *International Journal of Reproductive Biomedicine* 2016;**14**(10):643-8.

Mizrachi 2017 *{published data only}*

* Mizrachi Y, Dekalo A, Gluck O, Miremberg H, Dafna L, Feldstein O, et al. Single versus repeat doses of misoprostol for treatment of early pregnancy loss-a randomized clinical trial. *Human Reproduction* 2017;**32**(6):1202-7.

Mizrachi Y, NCT02515604. Comparison of single and repeated dose of vaginal misoprostol for the treatment of early pregnancy failure - a randomized clinical trial. https://clinicaltrials.gov/ct2/show/NCT02515604 2015.

Moran 2005 *{published data only}*

Moran T, Deutsch R. Methotrexate/misoprostol vs. a more standard approach for termination of pregnancies of undetermined location: a randomized, controlled trial. *Journal of Reproductive Medicine* 2005;**50**(10):784-92.

Mostafa-Gharebaghi 2010 *{published data only}*

Mostafa-Gharebaghi P, Mansourfar M, Sadeghi-Bazargani H. Low dose vaginal misoprostol versus prostaglandin E2 suppository for early uterine evacuation: a randomized clinical trial. *Pakistan Journal of Biological Sciences* 2010;**13**(19):946-50.

Mulayim 2009 *{published data only}*

Mulayim B, Celik NY, Onalan G, Zeyneloglu HB, Kuscu E. Sublingual misoprostol after surgical management of early termination of pregnancy. *Fertility & Sterility* 2009;**92**(2):678-81.

Nakintu 2001 *{published data only}*

Nakintu N. A comparative study of vaginal misoprostol and intravenous oxytocin for induction of labour in women with intra uterine fetal death in Mulago Hospital, Uganda.[see comment]. *African Health Sciences* 2001;**1**(2):55-9.

Nasrollahi 2008 *{published data only}*

Nasrollahi S, Arab M, Zamani M, Ghafeleh-Bashi M. Comparison between intravenous and intramuscular administration of prostaglandin E2 on management of missed abortion. *Journal of Research in Health Sciences* 2008;**8**(2):51-4.

Nassar 2005 *{published data only}*

Nassar AH//NCT00141895. A randomized trial of two regimens of misoprostol for second trimester termination for intrauterine fetal death. clinicaltrials.gov/ct2/show/NCT00141895 (first received 1 September 2005).

Nauman 2016 *{published data only}*

Nauman D, Saif N, Siddique U, Faruqi NJ. Comparison of manual vacuum aspiration with electrical vacuum aspiration in management of first trimester miscarriages. *Pakistan Journal of Medical and Health Sciences* 2016;**10**(2):503-6.

NCT00426491 2007 *{published data only}*

NCT00426491. Misoprostol for non-viable pregnancies. https://clinicaltrials.gov/show/nct00426491 2007.

NCT00670761 2008 *{published data only}*

NCT00670761. Misoprostol for the treatment of incomplete abortion: comparison of treatment options. https://clinicaltrials.gov/ct2/show/NCT00670761 2008.

NCT00797693 2008 *{published data only}*

NCT00797693. Misoprostol in termination of first trimester missed abortion. Https://clinicaltrials.gov/show/nct00797693 2008.

NCT02141555 2014 *{published data only}*

NCT02141555. Comparing buccal and vaginal misoprostol in management of early pregnancy loss. Https://clinicaltrials.gov/show/nct02141555 2014.

NCT02342002 2015 *{published data only}*

NCT02342002. Mifepristone and misoprostol versus misoprostol alone for missed abortion: a randomized-controlled trial. https://clinicaltrials.gov/ct2/show/NCT02342002 2015.

NCT02580175 2015 *{published data only}*

NCT02580175. Surgical evacuation of first trimester missed miscarriage with or without use of transabdominal ultrasound. https://clinicaltrials.gov/ct2/show/NCT02580175 2015.

NCT02957305 2016 *{published data only}*

NCT02957305. Misoprostol 400 µg versus 200 µg for cervical ripening in 1st trimester miscarriage. Https://clinicaltrials.gov/show/nct02957305 2016.

NCT03148314 2017 *{published data only}*

NCT03148314. Vaginal misoprostol in management of first trimester missed abortion. https://clinicaltrials.gov/show/nct03148314 2017.

NCT03148561 2017 *{published data only}*

Ali MK, NCT03148561. Misoprostol Versus Expectant Management in Women With Incomplete First-trimester Miscarriage After Misoprostol Treatment: A Randomized Clinical Trial.

https://clinicaltrials.gov/ct2/show/NCT03148561 2017.

NCT03148561. Management of women with an incomplete evacuation. https://clinicaltrials.gov/show/nct03148561 2017.

NCT03230825 2017 *{published data only}*

NCT03230825. Oral contraceptive pills versus expectant management for retained pregnancy products after a first trimester miscarriage: a randomized clinical trial. https://clinicaltrials.gov/ct2/show/NCT03230825 2017.

NCT03628625 2018 *{published data only}*

NCT03628625. Letrozole pretreatment with misoprostol for induction of abortion in first-trimester missed miscarriage. https://clinicaltrials.gov/show/nct03628625 2018.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Ng 2015 *{published data only}*

Ng BK, Annamalai R, Lim PS, Aqmar Suraya S, Nur Azurah AG, Muhammad Abdul Jamil MY. Outpatient versus inpatient intravaginal misoprostol for the treatment of first trimester incomplete miscarriage: a randomised controlled trial. *Archives of Gynecology and Obstetrics* 2015;**291**:105-13.

Ngoc 2004 *{published data only}*

Ngoc NT, Blum J, Westheimer E, Quan TV, Winikoff B. Medical treatment of missed abortion using misoprostol. *International Journal of Gynecology & Obstetrics* 2004;**87**:138-42.

Nguyen 2005 *{published data only}*

Nguyen TN, Blum J, Durocher J, Quan TT, Winikoff B. A randomized controlled study comparing 600 versus 1,200 micrograms oral misoprostol for medical management of incomplete abortion. *Contraception* 2005;**72**(6):438-42.

Niederauer 2018 *{published data only}*

Niederauer C, Pezzali L, Selbach T, De Paula Gudes Neto E, Maissiat J, Savaris R. Comparing the 200mug vs 400mug of the new vaginal misoprostol tablets for 1st trimester miscarriage. *International Journal of Gynecology and Obstetrics* 2018;**143**(S3):363.

Niromanesh 2005 *{published data only}*

Niromanesh S, Hashemi-Fesharaki M, Mosavi-Jarrahi A. Second trimester abortion using intravaginal misoprostol. *International Journal of Gynecology & Obstetrics* 2005;**89**:276-7.

Nor 2006 *{published data only}*

Nor Azlin MI, Abdullah HS, Zainul Rashid MR, Jamil MA. Misoprostol (alone) in second trimester terminations of pregnancy: as effective as Gemeprost? *Journal of Obstetrics and Gynaecology* 2006;**26**(6):546-9.

Nuthalapaty 2005 *{published data only}*

Nuthalapaty F, Ramsey P, Biggio J, Owen J. Comparative efficacy of high dose vaginal misoprostol for mid-trimester labor induction [abstract]. *American Journal of Obstetrics and Gynecology* 2004;**191**(6 Suppl 1):S73.

* Nuthalapaty FS, Ramsey PS, Biggio JR, Owen J. High-dose vaginal misoprostol versus concentrated oxytocin plus low-dose vaginal misoprostol for midtrimester labor induction: a randomized trial. *American Journal of Obstetrics and Gynecology* 2005;**193**(3 Pt 2):1065-70.

Nuutila 1997 *{published data only}*

Nuutila M, Toivonen J, Ylikorkala O, Halmesmaki E. A comparison between two doses of intravaginal misoprostol and gemeprost for induction of second-trimester abortion. *Obstetrics & Gynecology* 1997;**90**(6):896-900.

Ogden 2004 *{published data only}***ISRCTN21348449**

Ogden J//ISRCTN21348449. A pragmatic randomised control trial of expectant versus surgical management of first trimester spontaneous miscarriage. isrctn.com/ISRCTN21348449 (first received 23 January 2004).

Owen 1999 *{published data only}*

Owen J, Hauth JC. Vaginal misoprostol vs. concentrated oxytocin plus low-dose prostaglandin E2 for second trimester pregnancy termination. *Journal of Maternal-Fetal Medicine* 1999;**8**(2):48-50.

Pang 2001 *{published data only}*

* Pang MW, Chung T. Incomplete miscarriage: a randomized controlled trial comparing oral with vaginal misoprostol for medical evacuation. *Human Reproduction* 2001;**16**(11):2283-7.

Pang SM, Chung TK. A randomized clinical trial comparing oral and vaginal misoprostol for medical evacuation of spontaneous abortion [abstract]. *XVI FIGO World Congress of Obstetrics & Gynecology; 2000 Sept 3-8; Washington DC, USA* 2000;**Book 3**:69.

Pansky 2011 *{published data only}*

Pansky M, Fuchs N, Ben AI, Tovbin Y, Halperin R, Vaknin Z, et al. Intercoat (Oxiplex/AP Gel) for preventing intrauterine adhesions following operative hysteroscopy for suspected retained products of conception - A pilot study. *Journal of Minimally Invasive Gynecology* 2011;**18**(6 Suppl 1):S21.

Paraskevaides 1992 *{published data only}*

Paraskevaides E, Prendiville W, Stuart B, Scanaill SN, Walsh D, McGuinness N, et al. Medical evacuation of first trimester (twelve weeks gestation) incomplete abortion and missed abortion. *Journal of Gynecologic Surgery* 1992;**8**(3):159-63.

Paritakul 2010 *{published data only}*

Paritakul P, Phupong V. Comparative study between oral and sublingual 600 microg misoprostol for the treatment of incomplete abortion. *Journal of Obstetrics and Gynaecology Research* 2010;**36**(5):978-83.

Perry 1999 *{published data only}*

Perry KG, Rinehart BK, Terrone DA, Martin RW, May WL, Roberts WE. Second-trimester uterine evacuation: a comparison of intra-amniotic (15S)-15-methyl-prostaglandin F2alpha and intravaginal misoprostol. *American Journal of Obstetrics and Gynecology* 1999;**181**:1057-61.

Petersen 2013 *{published data only}*

ACTRN12612000150842. The Medical Management of Miscarriage Study: a randomized controlled clinical trial to determine the optimal dose of misoprostol for medical management of miscarriage before 13 weeks. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12612000150842 2012.

* Petersen SG, Perkins A, Gibbons K, Bertolone J, Devenish-Meares P, Cave D, et al. Can we use a lower intravaginal dose of misoprostol in the medical management of miscarriage? A randomised controlled study. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 2013;**53**(1):64-73.

Phupong 2004 *{published data only}*

Phupong V, Taneepanichskul S, Kriengsinyot R, Sriyirojana N, Blanchard K, Winikoff B. Comparative study between single dose 600 mg and repeated dose oral misoprostol for treatment of incomplete abortion. *Contraception* 2004;**70**:307-11.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Piotrowski 1979 *{published data only}*

Piotrowski J, Basta A, Klimczyk K, Malolepazy A, Dluzniewska M, Splawinski JA. Indomethacin increases abortifacient effect of PGE2 in man. *Prostaglandins* 1979;**17**:451-9.

Pomeranz 2016 *{published data only}*

Pomeranz M, NCT02917785. Testing the efficiency of Karman Curette in the treatment of misoprostol failure in women with missed abortion. https://clinicaltrials.gov/ct2/show/NCT02917785 2016.

Pongsatha 2004 *{published data only}*

Pongsatha S, Tongsong T. Intravaginal misoprostol for pregnancy termination. *International Journal of Gynecology & Obstetrics* 2004;**87**:176-7.

Prasartsakulchai 2004 *{published data only}*

Prasartsakulchai C, Tannirandorn Y. A comparison of vaginal misoprostol 800 microg versus 400 microg in early pregnancy failure: a randomized controlled trial. *Journal of the Medical Association of Thailand* 2004;**87 Suppl 3**:S18-23.

Promwangkwa 2017 *{published data only}*

Promwangkwa K, Puntitpong B, Chirdchim W, Sananpanichkul P. Efficacy of sublingual misoprostol with or without loading vaginal misoprostol in second trimester termination of pregnancy: a randomized controlled trial. *Journal of the Medical Association of Thailand* 2017;**100**(10):1050-5.

Ragusa 1994 *{published data only}*

Ragusa A, Vignali MJ, Zanetta G, Norchi S, Zanini A. Pre-operative cervical preparation before first trimester missed abortion: a randomized controlled comparison between single or double intracervical administration of pge2 gel. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1994;**50**(5):267-9.

Rahimi-Sharbaf 2015 *{published data only}*

Rahimi-Sharbaf F, Adabi K, Valadan M, Shirazi M, Nekuie S, Ghaffari P, et al. The combination route versus sublingual and vaginal misoprostol for the termination of 13 to 24 week pregnancies: a randomized clinical trial. *Taiwanese Journal of Obstetrics & Gynecology* 2015;**54**(6):660-5.

Ramsey 2004 *{published data only}*

Ramsey PS, Savage K, Lincoln T, Owen J. Vaginal misoprostol versus concentrated oxytocin and vaginal PGE2 for second-trimester labor induction. *Obstetrics & Gynecology* 2004;**104**(1):138-45.

Rita 2006 *{published data only}*

Rita Gupta S, Kumar S. A randomised comparison of oral and vaginal misoprostol for medical management of first trimester missed abortion. *JK Science* 2006;**8**(1):35-8.

Rivero-Lopez 1998 *{published data only}*

Rivero-Lopez E, Marquez-Maraver F, Duenas-Diez JL, Cabezas-Sanchez B. Deferred miscarriage: effectiveness of intravaginal misoprostol versus laminaria stems [Aborto diferido: eficacia del misoprostol intravaginal versus la aplicaci=n de tallos de laminaria]. *Progresos de Obstetricia y Ginecologia* 1998;**41**:579-81.

Robledo 2007 *{published data only}*

Robledo C, Zhang J, Troendle J, Barnhart K, Creinin MD, Westhoff C, et al. Clinical indicators for success of misoprostol treatment after early pregnancy failure. *International Journal of Gynecology & Obstetrics* 2007;**99**(1):46-51.

Roy 2003 *{published data only}*

Roy G, Ferreira E, Hudon L, Marquette G. The efficacy of oral versus vaginal misoprostol for second-trimester termination of pregnancy: a double-blind, randomized, placebo controlled trial [abstract]. *American Journal of Obstetrics and Gynecology* 2003;**189**(6 Suppl 1):S70.

Ruangchainikhom 2006 *{published data only}*

Ruangchainikhom W, Phongphissanou E, Bhekasuta J, Sarapak S. Effectiveness of 400 or 600 micrograms of vaginal misoprostol for terminations of early pregnancies. *Journal of the Medical Association of Thailand* 2006;**89**(7):928-33.

Saciloto 2011 *{published data only}*

Saciloto MP, Konopka CK, Velho MT, Jobim FC, Resener EV, Muradas RR, et al. [Manual vacuum aspiration uterine treatment of incomplete abortion to 12 gestational weeks: an alternative to curettage]. [Portuguese] [Aspiracao manual intrauterina no tratamento do abortamento incompleto ate 12 semanas gestacionais: uma alternativa a curetagem uterina]. *Revista Brasileira de Ginecologia e Obstetricia* 2011;**33**(10):292-6.

Saeed 2018 *{published data only}*

Saeed S, Manzoor R, Tazion S, Butt F, Badar N. Misoprostol for 1st trimester miscarriage: efficacy of vaginal versus oral misoprostol. *Pakistan Journal of Medical and Health Sciences* 2018;**12**(2):849-52.

Saichua 2009 *{published data only}*

Saichua C, Phupong V. A randomized controlled trial comparing powdery sublingual misoprostol and sublingual misoprostol tablet for management of embryonic death or anembryonic pregnancy. *Archives of Gynecology and Obstetrics* 2009;**280**(3):431-5.

Salamalekis 1990 *{published data only}*

Salamalekis E, Loghis C, Kassanos D, Traka A, Zourlas PA. Comparison of extra-amniotic prostaglandin F2alpha and dinoprostone use for labor induction after second trimester intrauterine fetal death. In: Proceedings of 12th European Congress of Perinatal Medicine; 1990 Sept 11-14; Lyon, France. 1990:228.

Sewzie 2014 *{published data only}*

Sewzie B, IRCT2014101015905N2. Effect of sublingual, vaginal and oral misoprostol on treatment of missed abortion in the pregnant women in the first trimester; comparative study. http://en.irct.ir/trial/15026 2014.

Shaamash 2019 *{published data only}*

Shaamash AH, Khlifah EA, Esmail AM, Abdelmonem SG. Home -based extended low-dose oral misoprostol in management

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

of first-trimester pregnancy loss in low-resource communities: a randomized trial. *Journal of Obstetrics and Gynaecology of India* 2019 Dec;**69**(6):501-8. [CENTRAL: CN-01959476] [EMBASE: 628356452] [PMID: 31844364]

Shah 2010 *{published data only}*

Shah N, Azam SI, Khan NH. Sublingual versus vaginal misoprostol in the management of missed miscarriage. *JPMA - Journal of the Pakistan Medical Association* 2010;**60**(2):113-6.

Sharifzadeh 2015 *{published data only}*

Sharifzadeh FS, Dezfooli GA, Chagharvand MM, Azad Z. Comparison of the efficacy of glyceryl trinitrate and misoprostol on cervical ripening for curettage in pregnant women at first trimester. [Persian]. *Iranian Journal of Obstetrics, Gynecology and Infertility* 2015;**18**(174):6-11.

Shobeira 2007 *{published data only}*

Shobeira JM, Atashkhoii S. Second trimester pregnancy termination by intravaginal and parenteral form of prostaglandin E2 [abstract]. In: 31st British International Congress of Obstetrics and Gynaecology; 2007 July 4-6; London, UK. 2007:210.

Shochet 2012 *{published data only}*

Blandine T, Ouattara AZ, Coral A, Hassane C, Clotaire H, Dao B, et al. Oral misoprostol as first-line care for incomplete abortion in Burkina Faso. *International Journal of Gynecology and Obstetrics* 2012;**119**:166-9.

Fawole O, Diop A, Adeyanju AO, Aremu OT, Winikoff B. Misoprostol as first-line treatment for incomplete abortion at a secondary-level health facility in Nigeria. *International Journal of Gynecology and Obstetrics* 2012;**119**:170-3.

NCT01539408. Sublingual misoprostol versus standard surgical care for the treatment of incomplete abortion. https://clinicaltrials.gov/ct2/show/NCT01539408 2012.

* Shochet T, Diop A, Gaye A, Nayama M, Sall AB, Bukola F, et al. Sublingual misoprostol versus standard surgical care for treatment of incomplete abortion in five sub-Saharan African countries. *BMC Pregnancy and Childbirth* 2012;**12**:127.

Shokry 2009 *{published data only}*

Shokry M, Shahin AY, Fathalla MM, Shaaban OM. Oral misoprostol reduces vaginal bleeding following surgical evacuation for first trimester spontaneous abortion. *International Journal of Gynecology & Obstetrics* 2009;**107**(2):117-20.

Sonsanoh 2014 *{published data only}*

Sonsanoh A, Chullapram T. Comparison of sublingual and vaginal misoprostol for termination of early pregnancy failure: a randomized controlled trial. *Thai Journal of Obstetrics and Gynaecology* 2014;**22**(3):128-36.

Souizi 2020 *{published data only}*

Souizi B, Akrami R, Borzoee F, Sahebkar M. Comparison of the efficacy of sublingual, oral, and vaginal administration of misoprostol in the medical treatment of missed abortion during first trimester of pregnancy: a randomized clinical trial study. Journal of Research in Medical Sciences (first received 2020 Jul 27);**25**:72. [CENTRAL: CN-02199219] [PMID: 33088309]

Srikhao 2005 *{published data only}*

Srikhao N, Tannirandorn Y. A comparison of vaginal misoprostol 800 microg versus 400 microg for anembryonic pregnancy: a randomized comparative trial. *Journal of the Medical Association of Thailand* 2005;**88**(Suppl 2):S41-S47.

Sripramote 2000 *{published data only}*

Sripramote M, Chatsuphang W. A randomized comparison of oral and vaginal misoprostol for cervical priming before uterine curettage in the first trimester of pregnancy. *Vajira Medical Journal* 2000;**44**(3):207-15.

Su 2005 *{published data only}*

Su L-L, Biswas A, Choolani M, Kalaichelvan V, Singh K. A prospective, randomized comparison of vaginal misoprostol versus intra-amniotic prostaglandins for midtrimester termination of pregnancy. *American Journal of Obstetrics and Gynecology* 2005;**193**:1410-4.

Suchonwanit 1999 *{published data only}*

Suchonwanit P. Comparative study between vaginal misoprostol 200 mg and 400 mg in first trimester intrauterine fetal death and anembryonic gestation. *Thai Journal of Obstetrics and Gynaecology* 1999;**11**(4):263.

Surita 1997 *{published data only}*

Surita FG. Misoprostol versus laminaria for cervical ripening in intrauterine fetal death. *Acta Obstetricia et Gynecologica Scandinavica Supplement* 1997;**76**(167:2):32.

Sweed 2015 *{published data only}*

Sweed MS, NCT02401425. Use of letrozole pretreatment with misoprostol for first-trimester medical abortion: randomised controlled trial. https://clinicaltrials.gov/ct2/show/NCT02401425 2015.

Sweed 2018 *{published data only}*

Sweed MS, NCT03487354. Medical abortion with multiple vs single daily dose of misoprostol in first trimester miscarriage: a randomized clinical trial. https://clinicaltrials.gov/ct2/show/NCT03487354 2018.

Tam 2002 *{published data only}*

Tam WH, Lau WC, Cheung LP, Yuen PM, Chung TK. Intrauterine adhesions after conservative and surgical management of spontaneous abortion. *Journal of the American Association of Gynecologic Laparoscopists* 2002;**9**(2):182-5.

Tam 2005 *{published data only}*

Tam WH, Tsui MH, Lok IH, Yip SK, Yuen PM, Chung TK. Long-term reproductive outcome subsequent to medical versus surgical treatment for miscarriage. *Human Reproduction* 2005;**20**(12):3355-9.

Tan 1969 *{published data only}*

Tan PM, Ratnam SS, Quek SP. Vacuum aspiration in the treatment of incomplete abortion. *Journal of Obstetrics & Gynaecology of the British Commonwealth* 1969;**76**(9):834-6.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Tang 2003 *{published data only}*

Tang OS, Lau WN, Ng EH, Lee SW, Ho PC. A prospective randomized study to compare the use of repeated doses of vaginal with sublingual misoprostol in the management of first trimester silent miscarriage. *Human Reproduction* 2003;**18**(1):176-81.

Tang 2006 *{published data only}*

Tang OS, Ong CY, Tse KY, Ng EH, Lee SW, Ho PC. A randomized trial to compare the use of sublingual misoprostol with or without an additional 1 week course for the management of first trimester silent miscarriage. *Human Reproduction* 2006;**21**(1):189-92.

Tanha 2010 *{published data only}*

Tanha FD. Comparison of the efficacy of two routes of misoprostol administration (sublingual and vaginal) for termination of second trimester pregnancy. en.search.irct.ir/view/1614 (first received 28 November 2010).

Tanha 2010a *{published data only}*

Tanha FD, Feizi M, Shariat M. Sublingual versus vaginal misoprostol for the management of missed abortion. *Journal of Obstetrics and Gynaecology Research* 2010;**36**(3):525-32.

Tanha 2013 *{published data only}*

Tanha FD, Golgachi T, Niroomand N, Ghajarzadeh M, Nasr R. Sublingual versus vaginal misoprostol for second trimester termination: A randomized clinical trial. *Archives of Gynecology and Obstetrics* 2013;**287**(1):65-9.

Tasnim 2011 *{published data only}*

Tasnim N, Mahmud G, Fatima S, Sultana M. Manual vacuum aspiration: a safe and cost-effective substitute of Electric vacuum aspiration for the surgical management of early pregnancy loss. *Journal of the Pakistan Medical Association* 2011;**61**(2):149-53.

Tasnim 2014 *{published data only}*

Tasnim N, Fatima S, Mahmud G. Manual vacuum aspirator: a safe and effective tool for decentralization of post miscarriage care. *JCPSP, Journal of the College of Physicians & Surgeons - Pakistan* 2014;**24**(11):815-9.

Teymouri 2017 *{published data only}*

Teymouri B, IRCT2017070934981N1. Comparison of induction of abortion in the first trimester using misoprostol and misoprostol with estrogen priming. http://en.irct.ir/trial/26580 2017.

Thavarasah 1986 *{published data only}*

Thavarasah AS, Almohdzar SA. Prostaglandin (F2 alpha) in missed abortion Intravenous, extra-amniotic and intramuscular administration--a randomized study. *Biological Research in Pregnancy and Perinatology* 1986;**7**:106-10.

Thida 2015 *{published data only}*

Thida M, Shwe MM, Htun KT, Maung NM, Khine EP, Win KS, et al. A randomised clinical trial comparing different routes of administration of repeated doses of 400ug misoprostol for management of missed miscarriages and anembryonic gestations in North Okkalapa General Hospital, Yangon, Myanmar. *BJOG: an international journal of obstetrics and gynaecology* 2015;**122**(Suppl S1):26-7.

Thong 2005 *{published data only}*

Mahmood TA, Shehata KI, Thong KJ. A randomized study of conservative management versus surgical uterine evacuation for incomplete miscarriage (Interim analysis) [abstract]. *XVI FIGO World Congress of Obstetrics & Gynecology; 2000 Sept 3-8; Washington DC, USA* 2000;**Book 3**:68-9.

Shehata KI, Thing KJ, Mahmood TA. Interim results of a random allocation study of conservative management versus uterine evacuation for incomplete miscarriage [abstract]. *Journal of Obstetrics and Gynaecology* 2000;**20**(1):105-6.

* Thong KJ, Mahmood TA, Shehata KI. A randomised trial comparing conservative management versus surgical uterine evacuation for first trimester miscarriage with retained products of conception. NHS Scotland (www.show.scot.nhs.uk/cso/Publications/ExecSumms/Oct_Nov02.htm) (accessed 3 March 2005) 2005.

Toppozada 1994 *{published data only}*

Toppozada MK, Shaala SA, Anwar MY, Haiba NA, Abdrabbo S, El-Absy HM. Termination of pregnancy with fetal death in the second and third trimesters - the double balloon versus extra-amniotic prostaglandin. *International Journal of Gynecology & Obstetrics* 1994;**45**:269-73.

Toptas 2011 *{published data only}*

Toptas T, Mendilcioglu I, Simsek M, Taskin O. Comparison of intravaginal misoprostol alone to combination of intravaginal misoprostol and extraamniotic Foley catheter for the second trimester of pregnancies. *American Journal of Obstetrics and Gynecology* 2011;**204**(1 Suppl):S126.

Torky 2018 *{published data only}*

Torky H, PACTR201701001973403. Misoprostol versus letrozole with misoprostol in the management of first trimester missed miscarriage. https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=1973 2017.

* Torky HA, Marie H, ElDesouky E, Gebreel S, Raslan O, Moussa AA, et al. Letrozole vs. placebo pretreatment in the medical management of first trimester missed miscarriage: a randomized controlled trial. *Geburtshilfe Und Frauenheilkunde* 2018;**78**(1):63-9.

Vafaei 2019 *{published data only}*

Vafaei H, IRCT20140317017034N7. Comparison between herbal medicine myrrh and expectant management for treatment of incomplete abortion. http://en.irct.ir/trial/39363 2019.

Van Mensel 2009 *{published data only}*

Van Mensel K, Claerhout F, Debois P, Keirse MJ, Hanssens M. A randomized controlled trial of misoprostol and sulprostone to end pregnancy after fetal death [Article ID 496320]. Obstetrics and Gynecology International 2009.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Wieringa-de 2002 *{published data only}*

Wieringa-De Waard M, Ankum W. The management of miscarriage: conservative management or curettage? [Het beleid bij een miskraam: afwachten of curettage?]. *Tijdschrift voor Fertiliteitsonderzoek* 2004;**18**(1):8-11.

* Wieringa-de Waard M, Vos J, Bonsel GJ, Bindels PJ, Ankum WM. Management of miscarriage: a randomized controlled trial of expectant management versus surgical evacuation. *Human Reproduction* 2002;**17**(9):2445-50.

Wijesinghe 2012 *{published data only}*

Wijesinghe PS, Herath RP, Abeysundara ID. A qualitative study on patients' perceptions of expectant management of first trimester incomplete miscarriage. *Ceylon Medical Journal* 2012;**57**(4):145-9.

Yapar 1996 *{published data only}*

Yapar EG, Senoz S, Urkutur M, Batioglu S, Gokmen O. Second trimester pregnancy termination including fetal death: comparison of five different methods. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1996;**69**:97-102.

Yilmaz 2005 *{published data only}*

Yilmaz B, Kelekci S, Ertas IE, Kahyaoglu S, Ozel M, Sut N, et al. Misoprostol moistened with acetic acid or saline for second trimester pregnancy termination: a randomized prospective double-blind trial. *Human Reproduction* 2005;**20**(11):3067-71.

Yilmaz 2007 *{published data only}*

Yilmaz B, Kelekci S, Ertas IE, Ozel M, Sut N, Mollamahmutoglu L, et al. Randomized comparison of second trimester pregnancy termination utilizing saline moistened or dry misoprostol. *Archives of Gynecology and Obstetrics* 2007;**276**(5):511-6.

Zanganeh 2010 *{published data only}*

Zanganeh M// IRCT138902053797N1. Comparing the effects of multiple doses of misoprostol with single dose of misoprostol plus oxytocin in induction of second trimester abortion. en.search.irct.ir/view/2936 (first received 12 June 2010).

Zhang 2000 *{published data only}*

Zhang C, Cheng W. A contrastive analysis of the efficacy of misoprostol and li fan nuo in intermediate term of pregnancy. *Journal of Wuhan University of Science and Technology (Natural Science Edition)* 2000;**23**(4):409-11.

References to studies awaiting assessment

Fang 2009 *{published data only}*

Fang AH, Chen QF, Zheng W, Li Y, Chen RY. Termination of missed abortion in a combined procedure: a randomized controlled trial. *Journal of Reproduction and Contraception* 2009;**20**(1):45-9.

References to ongoing studies

ChiCTR1900023198 2019 *{published data only}*

ChiCTR1900023198. The incidence of intrauterine adhesion after ultrasound-guided manual vacuum aspiration (USG-MVA): a prospective randomized controlled trial. http://www.chictr.org.cn/showproj.aspx?proj=39134 2019.

ChiCTR-TRC-08000725 2008 *{published data only}*

ChiCTR-TRC-08000725. The physical and psychological outcomes of expectant management, surgical evacuation or medical evacuation with single dose 800 mcg vaginal misoprostol for women with first trimester miscarriage in a randomized controlled trial. http://www.chictr.org.cn/showproj.aspx?proj=8810 2008.

Economides 2004 *{published data only}*

Economides D, ISRCTN95867389. Non-surgical management of delayed miscarriage: a randomised trial. http://www.isrctn.com/ISRCTN95867389 2004.

Ethayarooban 2017 *{published data only}*

Ethayarooban E, SLCTR/2017/023. Safety and effectiveness of vacuum aspiration, compared to curettage for management of patients with first trimester miscarriage in a limited resource setting in Sri Lanka. https://slctr.lk/trials/slctr-2017-023 2017.

EUCTR2007-007661-20-SE *{published data only}*

EUCTR2007-007661-20-SE. Which is the optimal treatment for miscarriage with a gestational sac in the uterus and which factors can predict if the treatment will be successful? https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-007661-20 2008.

ISRCTN11046192 2020 *{published data only}*

ISRCTN11046192. Efficacy of mifepristone followed by misoprostol compared to misoprostol alone in first-trimester miscarriage treatment [The role of Mifepristone on First-trimester miscarriage Treatment (MiFirsT) â€“ a double-blind randomized controlled trial]. Http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN11046192 (first received 2020). [CENTRAL: CN-02188308]

Kopalakrishnan 2014 *{published data only}*

Kopalakrishnan M, SLCTR/2014/029. Surgical, medical or expectant management of first trimester miscarriage and its implications on clinical and psychological outcomes - a randomized controlled trial. https://slctr.lk/trials/slctr-2014-029 2014.

Otieno 2018 *{published data only}*

Otieno V, PACTR201810731753052. Outcomes of medical versus surgical management of first trimester incomplete abortion on among women admitted at Kampala International University Teaching Hospital (KIU -TH). https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=4665 2018.

PACTR202009610896579 2020 *{published data only}*

PACTR202009610896579. Misoprostol versus manual vacuum aspiration for the treatment of first trimester incomplete miscarriage at university of Maiduguri teaching hospital. a

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

randomized controlled study. Http://www.who.int/trialsearch/Trial2.aspx?TrialID=PACTR202009610896579 (first received 2020). [CENTRAL: CN-02189183]

PACTR202009857889210 2020 *{published data only}*

PACTR202009857889210. Sublingual misoprostol versus manual vacuum aspiration for treatment of incomplete abortion in Nigeria: a randomized control study [Misoprostol for incomplete miscarriage]. Http://www.who.int/trialsearch/Trial2.aspx?TrialID=PACTR202009857889210 (first received 2020). [CENTRAL: CN-02189210] [PMID: -]

Sutharshan 2017 *{published data only}*

Sutharshan R, SLCTR/2017/014. Effectiveness of manual vacuum aspiration when compared to expectant care in achieving complete miscarriage in women with first trimester pregnancy loss - a randomized controlled trial. https://slctr.lk/trials/slctr-2017-014 2017.

Unkels 2008 *{published data only}***ISRCTN65305620**

Unkels R//ISRCTN65305620. Is misoprostol a safe alternative to manual vacuum aspiration in women with early pregnancy failure in a low resource setting? A randomized controlled trial. isrctn.com/ISRCTN65305620 (first received 22 February 2008).

Additional references

Alberman 1992

Alberman E. Spontaneous abortions: epidemiology. In: Stabile I, Grudzinskas JG, Chard T, editors(s). Spontaneous Abortion: Diagnosis and Treatment. London: Springer-Verlag, 1992:9-20.

Al Wattar 2019

Al Wattar BH, Murugesu N, Tobias A, Zamora J, Khan KS. Management of first-trimester miscarriage: a systematic review and network meta-analysis. *Human Reproduction Update* 2019;**25**(3):362-74.

Brignardello-Petersen 2018

Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al, GRADE Working Group. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *Journal of Clinical Epidemiology* 01/01/2018;**93**:36-44. [https://doi.org/10.1016/j.jclinepi.2017.10.005]

Caldwell 2005

Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;**331**(7521):897-900.

Caldwell 2010

Caldwell DM, Welton NJ, Ades AE. Mixed treatment comparison analysis provides internally coherent treatment effect estimates based on overviews of reviews and can reveal inconsistency. *Journal of Clinical Epidemiology* 2010;**63**(8):875-82.

Conway 2000

Conway K, Russell G. Couples' grief and experience of support in the aftermath of miscarriage. *British Journal of Medical Psychology* 2000;**73**(Pt 4):531-45.

Davies 2001

Davies NM, Longstreth J, Jamali F. Misoprostol therapeutics revisited. *Pharmacotherapy* 2001;**21**(1):60-73.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177-88.

Dias 2013

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Medical Decision Making* 2013;**33**(5):641-56.

Geller 2001

Geller PA, Klier CM, Neugebauer R. Anxiety disorders following miscarriage. *Journal of Clinical Psychiatry* 2001;**62**(6):432–8.

Higgins 2002

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539-58.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2012

Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* 2012;**3**:98-110.

Kim 2017

Kim C, Barnard S, Neilson JP, Hickey M, Vazquez JC, Dou L. Medical treatments for incomplete miscarriage. *Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No: CD007223. [DOI: 10.1002/14651858.CD007223.pub4]

Lemmers 2019

Lemmers M, Verschoor MA, Kim BV, Hickey M, Vazquez JC, Mol BW, Neilson JP. Medical treatment for early fetal death (less than 24 weeks). *Cochrane Database of Systematic Reviews* 2019, Issue 6. Art. No: CD002253. [DOI: 10.1002/14651858.CD002253.pub4]

MBRRACE-UK 2016

Knight M, Tuffnell D, Kenyon S, Shakespeare J, Gray R, Kurinczuk JJ, (Eds) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Surveillance of Maternal Deaths in the UK 2012-14 and Lessons Learned to Inform Maternity Care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-14. Oxford: National Perinatal Epidemiology Unit, University of Oxford, 2016.

Nanda 2012

Nanda K, Lopez LM, Grimes DA, Peloggia A, Nanda G. Expectant care versus surgical treatment for miscarriage. *Cochrane Database of Systematic Reviews* 2012, Issue 3. Art. No: CD003518. [DOI: 10.1002/14651858.CD003518.pub3]

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Neugebauer 1997

Neugebauer R, Kline J, Shrout P, Skodol A, O'Connor P, Geller PA, et al. Major depressive disorder in the 6 months after miscarriage. *JAMA* 1997;**277**(5):383-8.

NICE 2019

National Institute for Health and Clinical Excellence. Ectopic pregnancy and miscarriage: diagnosis and initial management. https://www.nice.org.uk/guidance/ng126 April 17, 2019.

Puhan 2014

Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;**349**:g5630.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Salanti 2011

Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple treatment meta-analysis: An overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**(2):163-71.

Schaff 2005

Schaff EA, DiCenzo R, Fielding SL. Comparison of misoprostol plasma concentrations following buccal and sublingual administration. *Contraception* 2005;**71**(1):22-5.

Shiers 2003

Shiers C. Abnormalities of early pregnancy. In: Myles' Textbook for Midwives. 14th edition. Churchill Livingstone, 2003.

StataCorp. 2019 [Computer program]

Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.. College Station, TX: StataCorp, 2019.

Tuncalp 2010

Tunçalp Ö, Gülmezoglu AM, Souza JP. Surgical procedures for evacuating incomplete miscarriage. *Cochrane Database of Systematic Reviews* 2010, Issue 9. Art. No: CD001993. [DOI: 10.1002/14651858.CD001993.pub2]

Tunçalp 2012

Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. *Cochrane Database of Systematic Reviews* 2012, Issue 8. Art. No: CD000494. [DOI: 10.1002/14651858.CD000494.pub4]

Turner 2012

Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International Journal of Epidemiology* 2012;**41**(3):818-27.

Veroniki 2013

Veroniki AA, Vasiliadis HS, Higgins JP, Georgia S. Evaluation of inconsistency in networks of interventions. *International Journal of Epidemiology* 2013;**42**(1):332–45.

Vogel 2019

Vogel JP, Dowswell T, Lewin S, Bonet M, Hampson L, Kellie F, et al. Developing and applying a 'living guidelines' approach to WHO recommendations on maternal and perinatal health. *BMJ Global Health* 2019;**4**:e001683.

White 2011

White I. Multivariate random-effects meta-regression: Updates to mvmeta. *Stata Journal* 2011;**11**(2):255-70.

White 2012

White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: Model estimation using multivariate meta-regression. *Research Synthesis Methods* 2012;**3**(2):111-25.

White 2015

White IR. Network meta-analysis. *Stata Journal* 2015;**15**:4.

WHO 2009

World Health Organization 2009. Integrated management for emergency and essential surgical care (IMEESC) toolkit. www.who.int/surgery/publications/imeesc/en/ (accessed 10 March 2017).

WHO 2012

World Health Organization. WHO Generic essential emergency equipment list. https://www.who.int/surgery/publications/s15982e.pdf 2012.

WHO 2012a

World Health Organization. Safe abortion: technical and policy guidance for health systems. https://www.who.int/reproductivehealth/publications/unsafe_abortion/9789241548434/en/.

WHO 2018

World Health Organization. Medical management of abortion. Geneva: WHO, 2018. [IGO Licence: CC BY-NC-SA 3.0 IGO]

WHO 2019

World Health Organization. World Health Organization Model List of Essential Medicines, 21st List, 2019. https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06 23rd July 2019.

References to other published versions of this review

Gallos 2017

Gallos ID, Williams HM, Price MJ, Eapen A, Eyo MM, Tobias A, et al. Methods for managing miscarriage: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2017, Issue 3. Art. No: CD012602. [DOI: 10.1002/14651858.CD012602]

* Indicates the major publication for the study

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abdelaleem 2020

Study characteristics		
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial	
Participants	84 women attending a university hospital in Egypt between July 2017 and July 2019 with a first trimester miscarriage (exact gestation unspecified) (incomplete miscarriage only)	
Interventions	Misoprostol 800 micrograms given vaginally as an outpatient versus expectant management as an outpatient	
Outcomes	Complete miscarriage	
Notes	Conference abstract only, source of funding not stated, declarations of interest not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being expectant management
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	>10% of women lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available. No contact details available.
Other bias	Low risk	No other sources of bias noted

Al-Maani 2014

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Al-Maani 2014 *(Continued)*

Participants	234 women attending a university hospital in Germany between February 2011 and April 2012 with a miscarriage of ≤13 weeks of gestation (both incomplete and missed miscarriage)
Interventions	Suction aspiration as an inpatient versus expectant management as an outpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; days of bleeding
Notes	Corresponding author emailed on 01-Apr-2019 to clarify nature of surgical treatment, however, no response was received from the corresponding author after 2 emails. It is the judgement of the authors the surgical intervention was most likely suction aspiration. Source of funding not stated, no declarations of interest.

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)	Low risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible due to one arm being expectant and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of participants lost to follow-up
Selective reporting (reporting bias)	Low risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other significant sources of bias noted

Ara 2009

Study characteristics

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	600 women attending a university hospital in Bangladesh between January 2007 and December 2008 with a miscarriage of ≤12 weeks gestation (both incomplete and missed miscarriage)
Interventions	Misoprostol given vaginally (exact dose and regimen not specified) versus suction aspiration
Outcomes	Data presented in an unusable form

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Ara 2009 *(Continued)*

Notes	Abstract only, no corresponding author details available, data presented in an unusable form. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available. No contact details available.
Other bias	Low risk	No other sources of bias noted

Arellano 2009

Study characteristics

Methods	Multi-centre, 2-arm, unblinded, randomised controlled trial
Participants	242 women attending a tertiary maternity hospital or a small private family planning clinic in Ecuador between unspecified dates with a miscarriage (exact gestation unspecified) (incomplete miscarriage only)
Interventions	Misoprostol 600 micrograms given orally as an outpatient versus suction aspiration as an outpatient manual procedure
Outcomes	Complete miscarriage; women's views/satisfaction
Notes	Abstract only, no corresponding author details available. Source of funding not stated, declarations of interest not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Arellano 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	>10% of women lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available. No contact details available.
Other bias	Low risk	No other sources of bias noted

Arif 2018

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	90 women attending a teaching hospital in Pakistan between August 2017 and February 2018, with a miscarriage of <12 weeks gestation (type of miscarriage unspecified)
Interventions	Suction aspiration as an outpatient manual procedure versus dilatation and curettage as an inpatient
Outcomes	Complete miscarriage; mean duration of hospital stay
Notes	Corresponding author emailed on 04-Jul-2019 to clarify type of miscarriage but no response was received from the corresponding author after 2 emails. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Draw method of randomisation used
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation sequence was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to both arms being surgical and one arm being under local anaesthetic and other arm being under general anaesthetic surgical
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated if outcome assessors were blinded

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Arif 2018 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other significant sources of bias noted

Bagratee 2004

Study characteristics		
Methods	Single-centre, 2-arm, double-blinded, randomised, placebo-controlled trial	
Participants	104 women presenting to a university hospital in the UK between August 2001 and March 2002 with a miscarriage of <13 weeks gestation (both incomplete and missed miscarriage)	
Interventions	Misoprostol 600 micrograms given vaginally (as a single dose on day 1 and if needed day 2) as an outpatient versus placebo given vaginally (as a single dose on day 1 and if needed day 2) as an outpatient	
Outcomes	Complete miscarriage; composite outcome of death or serious complication; pain scores; pelvic inflammatory disease, endometritis or sepsis; women's views/satisfaction; duration of bleeding; nausea; vomiting; diarrhoea; pyrexia	
Notes	Source of funding not stated, declarations of interest not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer based allocation to either arm
Allocation concealment (selection bias)	Low risk	Consecutively-numbered, sealed envelopes created by a third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel blinded to intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Bagratee 2004 *(Continued)*

Other bias	Low risk	No other significant sources of bias noted

Bique 2007

Study characteristics		
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial	
Participants	247 women attending a tertiary hospital in Mozambique between December 2004 and January 2006, with a miscarriage of ≤ 12 weeks gestation (incomplete miscarriage only)	
Interventions	Misoprostol 600 micrograms given orally as an outpatient versus suction aspiration as an outpatient manual procedure	
Outcomes	Complete miscarriage; need for unplanned/ emergency surgical procedure; pain scores; pelvic inflammatory disease, endometritis or sepsis; women's views/ satisfaction; nausea; vomiting; pyrexia	
Notes	Source of funding not stated, declarations of interest not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-based randomisation
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	>10% lost at follow-up with nearly double lost from the suction curettage arm compared to the misoprostol arm
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Blohm 2005

Study characteristics		
Methods	Single-centre, 2-arm, double-blinded, randomised, placebo-controlled trial	

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Blohm 2005 *(Continued)*

Participants	126 women attending a university hospital in Sweden between unspecified dates, with a miscarriage in the first trimester (exact gestation unspecified) (type of miscarriage unspecified)
Interventions	Misoprostol 400 micrograms given vaginally as an outpatient versus placebo given vaginally as an outpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complication; pain scores; pelvic inflammatory disease, sepsis or endometritis
Notes	Source of funding not stated, declarations of interest not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used for sequence generation
Allocation concealment (selection bias)	Low risk	Sealed numbered enveloped created by a third party used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel blinded to intervention. Placebo and misoprostol identical looking
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation list not kept by trial team and not broken until after completion of study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Braham 2016

Study characteristics

Methods	Single-centre, 2 arm, unblinded, randomised controlled trial
Participants	60 women attending a tertiary hospital in the Bahamas between April 2007 and October 2007, with a miscarriage in the first trimester (exact gestation unspecified) (incomplete miscarriage only)
Interventions	Misoprostol 400 micrograms given orally (every 4 hours for 3 doses in total) as an outpatient versus suction aspiration
Outcomes	Days of bleeding
Notes	Abstract only available, no corresponding author details or full text available. Source of funding not stated, declarations of interest not stated.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Braham 2016 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated how random sequence was achieved
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of patients in surgical group not clearly stated.
Selective reporting (reporting bias)	Unclear risk	No protocol or full text available, complete miscarriage rate only reported for one intervention
Other bias	Low risk	No other sources of bias noted

Caceres 1979

Study characteristics	
Methods	Single-centre, 4-arm, unblinded, randomised controlled trial
Participants	600 women attending a tertiary hospital in El Salvador between April 1978 and May 1979 with a miscarriage of ≤ 14 weeks gestation (incomplete miscarriage only)
Interventions	Dilatation and curettage versus suction aspiration
Outcomes	Complete miscarriage; composite outcome of death of serious complication; pelvic inflammatory disease, endometritis or sepsis; cervical tear; mean duration of hospital stay; readmission to hospital; pyrexia
Notes	Study performed with 4 arms with randomisation between inpatient and outpatient settings as well as the two different intervention but these groups were combined for purposes of this review into the interventions above. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Caceres 1979 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to both arms being surgical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	24% lost to analysis due to reassignment between study groups
Selective reporting (reporting bias)	Unclear risk	No protocol available for inspection but protocol is mentioned in text, no specific evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Caceres 1981

Study characteristics	
Methods	Single-centre, 4-arm, unblinded, randomised controlled trial
Participants	599 women attending a university maternity hospital in Columbia between April 1978 to September 1978, with a miscarriage of ≤ 15 weeks gestation (incomplete miscarriage only)
Interventions	Dilatation and curettage versus suction aspiration
Outcomes	Composite outcome of death or serious complication; re-admission to hospital; vomiting; pyrexia
Notes	It was noted by the authors that 98.7% of participants were ≤ 12 weeks of gestation therefore it was felt that as only a very small proportion of participants would be > 14 weeks and that the study should be included. Study performed with 4 arms with randomisation between inpatient and outpatient settings as well as the two different interventions but these groups were combined for purposes of this review into the interventions above. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Shuffled cards in sealed envelopes
Allocation concealment (selection bias)	Low risk	Sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to surgical nature of both intervention arms

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Caceres 1981 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Chigbu 2012

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	320 women attending a private clinic in Nigeria between January 2010 and December 2011 with a miscarriage of gestation ≤ 12 weeks (incomplete miscarriage only)
Interventions	Misoprostol 600 micrograms given orally as an outpatient versus suction aspiration as an outpatient manual procedure
Outcomes	Complete miscarriage; pain scores; women's views/ satisfaction; nausea; vomiting; diarrhoea; pyrexia
Notes	Source of funding not stated, declarations of interest not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated how random sequence was achieved
Allocation concealment (selection bias)	Low risk	Sequentially-numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Chigbu 2012 *(Continued)*

Other bias	Low risk	No other sources of bias noted

Chipchase 1997

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	35 women attending a university hospital in the UK between unspecified dates, with a miscarriage of < 13 weeks gestation (incomplete miscarriage only)
Interventions	Suction aspiration as an inpatient electric procedure versus expectant management as an outpatient
Outcomes	Pelvic inflammatory disease, endometritis or sepsis; women's views/ satisfaction
Notes	Published short communication only, no up-to-date corresponding author details or full paper found. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated how random sequence was achieved
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being expectant and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Chu 2020

Study characteristics	
Methods	Multi-centre, 2-arm, blinded, placebo-controlled randomised controlled trial

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Chu 2020 *(Continued)*

Participants	711 women attending hospitals in the UK between Oct 2017 and July 2019 with a miscarriage of ≤12 weeks gestation (missed miscarriage only)
Interventions	Mifepristone 200 mg given orally or an oral placebo tablet, both followed by a single dose of vaginal, oral, or sublingual misoprostol 800 micrograms 2 days later.
Outcomes	Complete miscarriage; composite outcome of death or serious complication; infection; need for emergency surgery; days of bleeding.
Notes	Funded by the UK NIHR Health Technology Assessment program (project number HTA 15/160/02). Authors declare no relevant conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated in 1:1 ratio with the use of minimization.
Allocation concealment (selection bias)	Low risk	Through a secure, centralised Internet facility.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition bias was <10% and balanced across study arms.
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol (ISRCTN17405024) that was registered prospectively.
Other bias	Low risk	Funded by the UK NIHR Health Technology Assessment programme (project number HTA 15/160/02).

Chung 1997

Study characteristics

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	350 women attending a university hospital in Hong Kong between unspecified dates, with a miscarriage (exact gestation unspecified) (incomplete miscarriage only)
Interventions	Suction aspiration versus expectant management
Outcomes	Data presented in an unusable form

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Chung 1997 *(Continued)*

Notes	Abstract only, no corresponding author details available, data presented in an unusable form. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being expectant and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available. No contact details available.
Other bias	Low risk	No other sources of bias noted

Chung 1999

Study characteristics

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	635 women attending a university hospital in Hong Kong between October 1995 and January 1998, with a miscarriage (exact gestation unspecified but the mean gestation of each arm was < 11 weeks with a standard deviation of 2.6 for the suction aspiration group and 2.5 for the misoprostol group) (both incomplete and missed miscarriage)
Interventions	Misoprostol 400 micrograms given orally (every 4 hours for 3 doses in total) as an inpatient versus suction aspiration as an inpatient electric procedure
Outcomes	Complete miscarriage; composite outcome of death or serious complication; pelvic inflammatory disease, endometritis or sepsis; change in haemoglobin measurements before and after the miscarriage; days of bleeding; cervical tear; mean duration of hospital stay
Notes	Authored confirmed via email on 02-May-2019 that surgical arm was electric suction curettage +/- possible check curettage. Trial funded by Health Services Research Fund of Hong Kong. Declarations of interest not stated.

Risk of bias

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Chung 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated set of random numbers
Allocation concealment (selection bias)	Low risk	Serially-numbered, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% lost to follow-up at 2 weeks
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Dabash 2010

Study characteristics	
Methods	Multi-centre, 2-arm, unblinded, randomised controlled trial
Participants	697 women attending 2 tertiary hospitals in Egypt between 7th February 2007 and 28th October 2008, with a miscarriage of ≤12 weeks gestation (incomplete miscarriage only)
Interventions	Misoprostol 400 micrograms given sublingually as an outpatient versus suction aspiration as an outpatient or inpatient manual procedure
Outcomes	Complete miscarriage; change in haemoglobin measurements before and after the miscarriage; women's views/ satisfaction; nausea; vomiting; pyrexia
Notes	Study was funded by the David and Lucille Packard Foundation. The authors declare no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Remote, third party, computer-generated randomisation in blocks of 10
Allocation concealment (selection bias)	Low risk	Remotely created by a third party, sequentially-numbered envelopes

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Dabash 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Dangalla 2012

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	160 women attending a university hospital in Sri Lanka between 1st January 2009 to 15th July 2009 with a miscarriage of < 14 weeks gestation (incomplete miscarriage only)
Interventions	Expectant care as an inpatient versus suction aspiration as an inpatient electric procedure
Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/ emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; women's views/ satisfaction
Notes	Clinical Trials Register, Sri Lanka (SLCTR/2008/011). Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation used
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being expectant and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Dangalla 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Some results were only reported as a difference with a P-value not the actual results themselves.
Other bias	Low risk	No other sources of bias notes

Dao 2007

Study characteristics		
Methods	Multi-centre, 2-arm, unblinded, randomised controlled trial	
Participants	460 women attending 2 university hospitals in Burkina Faso between April 2004 and October 2004 with a miscarriage of < 12 weeks of gestation (incomplete miscarriage only)	
Interventions	Misoprostol 600 micrograms given orally as an outpatient versus suction aspiration as an outpatient manual procedure	
Outcomes	Complete miscarriage; composite outcome of death or serious complication; pain score; pelvic inflammatory disease, endometritis or sepsis; women's views/ satisfaction; re-admission to hospital; nausea; vomiting; pyrexia	
Notes	Source of funding not stated, declarations of interest not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Third-party, computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Third-party, sequentially-ordered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if all outcome assessors were blinded, only stated sonographers performing scans were not members of the study team
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	Funded by the Packard Foundation

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Das 2014

Study characteristics		
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial	
Participants	222 women attending a university hospital in Pakistan between May 2011 and April 2012 with a miscarriage of <12 weeks of gestation (incomplete miscarriage only)	
Interventions	Manual vacuum aspiration versus misoprostol 600 micrograms given orally as an outpatient	
Outcomes	Complete miscarriage; pyrexia	
Notes	Source of funding not stated, declarations of interest not stated; no evidence of prospective trial registration	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation using computer-generated random sequence,
Allocation concealment (selection bias)	Low risk	Treatment was printed on a card and that card was closed in a envelop. Envelopes were then sealed and were mixed randomly
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being surgical management and other arm being medical management
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% of women lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No other sources of bias noted

Davis 2007

Study characteristics	
Methods	Multi-centre, 2-arm, unblinded, randomised controlled trial
Participants	652 women attending 4 university medical centres in the USA between March 2002 and March 2004 with a miscarriage of ≤13 weeks gestation (both incomplete and missed miscarriage)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Davis 2007 *(Continued)*

Interventions	Misoprostol 800 micrograms given vaginally (as a single dose on day 1 and if needed day 3) as an outpatient versus suction aspiration either as an outpatient manual or inpatient electric procedure in a 3:1 ratio
Outcomes	Changes in haemoglobin measurements before and after the miscarriage
Notes	Is a secondary analysis of Zhang 2005. Funded by contracts (N01-HD-1-3321, N01- HD-3322, N01-HD-3323, N01-HD-3324, and N01-HD-3325) with the National Institute of Child Health and Human Development, National Institutes of Health. No declarations of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised, remote, computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Centralised, remote, computer-generated allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias notes

de Holanda 2003

Study characteristics

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	102 women attending a university hospital in Brazil between Jan 1998 and July 2001 with a miscarriage of ≤12 weeks gestation (type of miscarriage not specified)
Interventions	Suction curettage versus manual vacuum aspiration
Outcomes	Pain control, need of mechanical cervical dilation, time of evacuation of the uterus, rate of complications and hospital stay
Notes	Source of funding not stated, declarations of interest not stated. None of the reported outcomes were eligible for inclusion in the review.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

de Holanda 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated how random sequence was achieved
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to the two groups being surgical management
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol or full text available
Other bias	Unclear risk	No other sources of bias noted

de Jonge 1995

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	50 women attending a university hospital in South Africa between unspecified dates with a miscarriage of ≤ 14 weeks of gestation (incomplete miscarriage only)
Interventions	Misoprostol 400 micrograms given orally as an inpatient versus dilatation and curettage as an inpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complication
Notes	Short communication only available, no corresponding author contact details or full paper available. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, random numbers
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes used

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

de Jonge 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol mentioned but not available for review. No evidence of selective reporting.
Other bias	Low risk	No other sources of bias noted

Demetroulis 2001

Study characteristics		
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial	
Participants	80 women attending a secondary hospital in the UK between unspecified dates, with a miscarriage of <13 weeks gestation (both incomplete and missed miscarriage)	
Interventions	Misoprostol 800 micrograms given vaginally as an inpatient versus suction aspiration as an inpatient electric procedure	
Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; women's views/satisfaction; nausea; vomiting; diarrhoea	
Notes	Source of funding not stated, declarations of interest not stated.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, random numbers
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if all outcome assessors were blinded

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Demetroulis 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Fernlund 2018

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	189 women attending a university hospital in Sweden between September 2008 and December 2015, with a miscarriage of 6 to 16 weeks gestation (missed miscarriage only)
Interventions	Misoprostol 800 micrograms given vaginally as an outpatient versus expectant management as an outpatient
Outcomes	Complete miscarriage; composite outcome of death of serious complication; need for unplanned/emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; days of bleeding; mean duration of hospital stay; re-admission to hospital; nausea; vomiting; diarrhoea
Notes	Clinicaltrials.gov identifier NCT01033903. Study terminated prematurely due to slower than anticipated recruitment despite a prolonged recruitment period. It was noted the maximum gestation age of the study was 16 weeks, however, the mean gestational age in weeks of the misoprostol arm was 10.9 with a standard deviation of 2.0 and the mean gestational age in weeks of the expectant arm was 10.8 with a standard deviation of 1.8 and so it was felt by the authors that the vast majority of patients would have been ≤ 14 weeks gestation and therefore the paper was included. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Third-party, computer-generated, randomisation in blocks of 6
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, sealed, opaque envelopes prepared by a third party
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessor was unblinded
Incomplete outcome data (attrition bias)	Low risk	< 10% lost to follow-up

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Fernlund 2018 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Outcomes listed in protocol have been reported
Other bias	Low risk	No other sources of bias noted

Fonseca 1997

Study characteristics		
Methods	Single-centre, 2-arm, randomised controlled trial	
Participants	30 women attending an unspecified healthcare facility in Brazil between 11th December 1995 and 4th January 1996 with a miscarriage of <12 weeks gestation (incomplete miscarriage only)	
Interventions	Dilatation and sharp curettage as an inpatient versus suction aspiration as an outpatient manual procedure	
Outcomes	Mean duration of hospital stay	
Notes	Translation only available at time of data extraction. Cochrane translation by Source of funding not stated, declarations of interest not stated.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated how random sequence was achieved
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation sequence was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated if participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if all outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	No other sources of bias noted

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Ganguly 2010

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	180 women attending a university hospital in India between 1st May 2007 and 30th April 2008, with a miscarriage of <12 weeks gestation (both incomplete and missed miscarriage only)
Interventions	Misoprostol 800 micrograms given vaginally (as a single dose on day 1 and if needed on day 3) as an outpatient versus suction aspiration as an inpatient manual procedure in a 2:1 ratio
Outcomes	Complete miscarriage; composite outcome of death or serious complication; cervical tear; nausea; diarrhoea; pyrexia
Notes	Source of funding not stated, declarations of interest not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, random number list
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol but no obvious selective reporting
Other bias	Low risk	No other sources of bias noted

Gazvani 2000

Study characteristics	
Methods	Single centre, 3-arm, unblinded, randomised controlled trial
Participants	22 women attending a maternity hospital in the UK between November 1998 and April 1999, with a miscarriage in the 1st trimester (exact gestation unspecified) (incomplete miscarriage only)
Interventions	Suction aspiration as a manual procedure versus expectant management
Outcomes	Data presented in an unusable form

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gazvani 2000 *(Continued)*

Notes	Abstract only, no corresponding author details available, medical management arm was also present for patients with missed miscarriage but medical management was not qualified and therefore this side of trial not included, results given for incomplete miscarriage side of trial do not make mathematical sense. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being expectant and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available. No contact details available.
Other bias	Low risk	No other sources of bias noted

Graziosi 2004

Study characteristics

Methods	Multi-centre, 2-arm, unblinded, randomised controlled trial
Participants	154 women attending three hospitals in the Netherlands between November 2001 and June 2003 with a miscarriage of between 6 and 14 weeks gestation (missed miscarriage only)
Interventions	Misoprostol 200 micrograms given vaginally, followed by misoprostol 800 micrograms given vaginally if needed versus suction aspiration
Outcomes	Complete miscarriage; need for emergency surgery; pain score; days of bleeding; nausea; diarrhoea
Notes	Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computer program with a block randomisation sequence

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Graziosi 2004 *(Continued)*

Allocation concealment (selection bias)	Low risk	A computer-based block randomisation sequence guaranteed the concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available. No contact details available.
Other bias	Unclear risk	No other sources of bias noted

Hamel 2021

Study characteristics	
Methods	Multi-centre, 2-arm, blinded, placebo-controlled randomised controlled trial
Participants	351 women attending hospitals in the Netherlands between June 2018 and January 2020 with a miscarriage of ≤14 weeks gestation (missed miscarriage only)
Interventions	Mifepristone 200 mg given orally or an oral placebo tablet, both followed by misoprostol 800 micrograms given orally 36 to 48 hours later.
Outcomes	Complete miscarriage; composite outcome of death or serious complication; infection; need for emergency surgery; diarrhoea; nausea
Notes	Funded by the (project number: 3080 B15191). In addition, departmental funds from the Department of Obstetrics and Gynaecology from both Radboud university medical centre and Canisius Wilhelmina Hospital, both Nijmegen, the Netherlands, were used. Dr. Hamel reports grants from Healthcare Insurers Innovation Foundation, during the conduct of the study; meant to cover costs of performing the trial, no involvement in any other aspect of the trial such as study design, data gathering/analysis, manuscript preparation. All other authors have nothing to declare.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was conducted by block randomisation, with a block size of eight, stratified by hospital. The randomisation tables were generated by two independent physicians, who had no further role in the execution of the trial.
Allocation concealment (selection bias)	Low risk	Through a secure, computerised system.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Hamel 2021 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and caregivers were blinded to treatment allocations.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment allocations.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition bias was <10% and balanced across study arms.
Selective reporting (reporting bias)	Low risk	The study report matches the study protocol (ISRCTN17405024) that was registered prospectively.
Other bias	Low risk	Funded by the Healthcare Insurers Innovation Foundation (project number: 3080 B15191). In addition, departmental funds from the Department of Obstetrics and Gynaecology from both Radboud university medical centre and Canisius Wilhelmina Hospital, both Nijmegen, the Netherlands, were used.

Harwood 2008

Study characteristics	
Methods	Multi-centre, 2-arm, unblinded, randomised controlled trial
Participants	652 women attending 4 university hospitals in the USA between March 2002 and March 2004 with a miscarriage of <12 weeks of gestation (both incomplete and missed miscarriage)
Interventions	Misoprostol 800 micrograms given vaginally (as a single dose on day 1 and if needed day 3) as an outpatient versus suction aspiration either as an outpatient manual or inpatient electric procedure in a 3:1 ratio
Outcomes	Pain scores; depression; anxiety
Notes	this is a secondary analysis of Zhang 2005. NICHD, National Institutes of Health (NIH), under contract numbers N01-HD-1-3321 through 3325 and by NIH General Clinic Research Center Grant MOIRR000056. Declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised, remote, computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Centralised, remote, computer-generated allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Harwood 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias notes

Ibiyemi 2018

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	200 women attending a teaching hospital in Nigeria between April 2014 and November 2015 with a miscarriage of < 13 weeks gestation (incomplete miscarriage only)
Interventions	Misoprostol 600 micrograms given orally as an inpatient versus suction aspiration as an inpatient manual procedure
Outcomes	Complete miscarriage; composite outcome of death or serious complication; women's views/ satisfaction; nausea; vomiting; diarrhoea; pyrexia
Notes	PACTR201803003087264. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Allocation concealed, statistician not involved in care
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	<10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol not able to be found but no obvious selective reporting

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Ibiyemi 2018 *(Continued)*

Other bias	Low risk	No other sources of bias noted

Igogo 2015

Study characteristics	
Methods	Multi-centre, 2-arm, unblinded, randomised controlled trial
Participants	260 women attending a district general hospital and a tertiary hospital in Kenya between unspecified dates, with a miscarriage (exact gestation unspecified) (incomplete miscarriage only)
Interventions	Suction aspiration as an outpatient manual procedure versus misoprostol 400 micrograms given sub-lingually as an outpatient
Outcomes	Data presented in an unusable form
Notes	Abstract only, no corresponding author details available, data presented in an unusable form. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available. No contact details available.
Other bias	Low risk	No other sources of bias noted

Kaluaarachchi 2015

Study characteristics	
Methods	Single-centre, 3-arm, unblinded, randomised controlled trial

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kaluaarachchi 2015 *(Continued)*

Participants	180 women attending a university hospital in Sri Lanka between unspecified dates, with a miscarriage in the first trimester (both incomplete and missed miscarriage)
Interventions	Suction aspiration versus medical management versus expectant management
Outcomes	Data presented in an unusable form
Notes	Abstract only, no corresponding author details available, medical management not qualified, data presented in an unusable form. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical, one arm being expectant and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available
Other bias	Low risk	No other sources of bias noted

Karlsen 2001

Study characteristics

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	97 women attending a women's Clinic in Norway between unspecified dates, with a miscarriage of ≤ 12 weeks gestation (type of miscarriage unspecified)
Interventions	Suction aspiration as an inpatient procedure versus expectant management as an outpatient
Outcomes	Complete miscarriage; pelvic inflammatory disease, endometritis or sepsis; days of bleeding
Notes	Email of corresponding author not in use anymore, article translated to English for data extraction from Norwegian. Source of funding not stated, declarations of interest not stated.

Risk of bias

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Karlsen 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated how random sequence of envelopes was achieved
Allocation concealment (selection bias)	Low risk	Closed envelopes were used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being surgical and other arm being expectant
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol but no obvious selective reporting
Other bias	Low risk	No other sources of bias noted

Kashif 2020

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	60 women attending a university hospital in Pakistan between August 2011 and August 2012 with a miscarriage of <12 weeks of gestation (incomplete and missed miscarriage)
Interventions	Misoprostol 800 micrograms given vaginally as an outpatient versus suction aspiration as an inpatient
Outcomes	Complete miscarriage; need for emergency surgery; infection; pyrexia; vomiting; diarrhoea
Notes	Source of funding not stated, declarations of interest not stated; no evidence of prospective trial registration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation achieved using block method, however block size not stated
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not stated
Blinding of participants and personnel (performance bias)	High risk	Not possible due to one arm being medical management and other arm being expectant management

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kashif 2020 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% of women lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No registered protocol or prospective trial registration available
Other bias	Low risk	No other sources of bias noted

Kittiwatanakul 2012

Study characteristics		
Methods	Single-centre, 2 arm, unblinded, randomised controlled trial	
Participants	94 women attending a hospital in Thailand between 1st March 2005 and 15th December 2009 with a miscarriage of < 13 weeks gestation (incomplete miscarriage only)	
Interventions	Suction aspiration as an outpatient electric procedure versus dilatation and curettage as an outpatient procedure	
Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; mean volume of blood loss	
Notes	Source of funding not stated, the authors declare no conflicts of interest.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, random number list used
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, opaque, sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to both arms being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kittiwatanakul 2012 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol but no obvious selective reporting
Other bias	Low risk	No other sources of bias noted

Kong 2013

Study characteristics		
Methods	Single-centre, 3-arm, unblinded, randomised controlled trial	
Participants	180 women attending a university-affiliated, tertiary hospital in Hong Kong between September 2008 and July 2010 with a miscarriage in the first trimester (exact gestation not specified) (both incomplete and missed miscarriage)	
Interventions	Suction aspiration as an inpatient procedure versus misoprostol 800 micrograms given vaginally as an outpatient versus expectant management as an outpatient	
Outcomes	Complete miscarriage; need for unplanned/ emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; change in haemoglobin measurements before and after the miscarriage; days of bleeding; readmission to hospital; vomiting; diarrhoea; pyrexia; anxiety score; depression score	
Notes	Source of funding not stated, declarations of interest not stated.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, random numbers used
Allocation concealment (selection bias)	Low risk	Personnel were unaware of randomisation schedule
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical, another being surgical and another being expectant
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol mentioned in text but not available for inspection. No obvious selective reporting
Other bias	Low risk	No other sources of bias noted

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kovavisarach 2002

Study characteristics		
Methods	Single-centre, 2-arm, single-blinded, randomised placebo-controlled trial	
Participants	54 women attending a tertiary hospital in Thailand between 1st July 1998 and 31st January 1999 with a miscarriage of ≤12 weeks gestation (missed miscarriage only)	
Interventions	Misoprostol 400 micrograms given vaginally as an outpatient versus placebo given vaginally as an outpatient	
Outcomes	Complete miscarriage; diarrhoea; pyrexia	
Notes	Source of funding not stated, declarations of interest not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated how patients were randomly allocated
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated if study personnel were blinded, it is assumed participants were blinded due to the use of a placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol but no obvious selective reporting
Other bias	Low risk	No other sources of bias noted

Kyaw 2015

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	108 women attending a teaching hospital in Myanmar between unspecified dates with a miscarriage (exact gestation not specified) (type of miscarriage not specified)
Interventions	Misoprostol 800 micrograms given vaginally as an inpatient versus dilatation and curettage as an inpatient
Outcomes	Complete miscarriage; mean volume of blood loss

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kyaw 2015 *(Continued)*

Notes	Abstract only, corresponding author details not available. The abstract states 800mg of misoprostol was used. It is assumed that the authors mean Mg to mean micrograms. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Lottery method used for randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation sequence unlikely to have been concealed due to lottery method
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% of participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol or full paper available but no obvious selective reporting
Other bias	Low risk	No other sources of bias noted

Lee 2001

Study characteristics

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	218 women attending a university teaching hospital in Hong Kong between October 1995 and June 1996 with a miscarriage (exact gestation not specified) (incomplete miscarriage only)
Interventions	Misoprostol 400 micrograms given orally (every 4 hours for 3 doses in total) as an inpatient versus dilatation and curettage as an inpatient
Outcomes	Depression score
Notes	It is assumed that when describing the medical arm in the full text the unit of measurement of pg was written in error and it was supposed to be micrograms, not picograms. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Lee 2001 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated, set of random numbers used
Allocation concealment (selection bias)	Low risk	Opaque, sequentially-numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	>10% lost to follow-up in each arm
Selective reporting (reporting bias)	High risk	No protocol available. Complete miscarriage not and other clinical outcomes not reported to give context for depression scores.
Other bias	Low risk	No other sources of bias noted

Lister 2005

Study characteristics	
Methods	Single-centre, 2-arm, double-blinded, randomised placebo-controlled trial
Participants	36 women attending a teaching hospital in the USA| between 15th February 2002 and 19th March 2003 with a miscarriage (exact gestation not stated) (missed miscarriage only)
Interventions	Misoprostol 800 micrograms given vaginally (as a single dose on day 1 and if needed day 2) as an outpatient versus placebo given vaginally (as a single dose on day 1 and if needed day 2)
Outcomes	Complete miscarriage; pain scores; women's views/ satisfaction; re-admission to hospital; nausea; vomiting; diarrhoea
Notes	Supported by the Riverside Methodist Hospital Medical Research Foundation, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence generated by the study epidemiologist in blocks
Allocation concealment (selection bias)	Low risk	Opaque randomisation packets used and both interventions similar in appearance
Blinding of participants and personnel (performance bias)	Low risk	Study personnel and participants blinded to intervention and placebo similar in appearance to misoprostol

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Lister 2005 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol or full text available but no obvious selective reporting
Other bias	Low risk	No other sources of bias noted

Machtinger 2002

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	66 women attending a medical centre in Israel between unspecified dates with a miscarriage of ≤ 9 weeks gestation (missed miscarriage only)
Interventions	Mifepristone 600 milligrams given orally + misoprostol 400 micrograms given orally 48 hours later and if needed repeat of misoprostol dose 3 hours later versus misoprostol 400 micrograms given orally + misoprostol 400 micrograms given orally 48 hours later and if needed repeat of misoprostol dose 3 hours later
Outcomes	Complete miscarriage; composite outcome of death or serious complications; need for unplanned/emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; pyrexia
Notes	Abstract only, no corresponding author details, It is assumed that the units of measurement for mifepristone (mcg) and misoprostol (mg) were written incorrectly in the abstract and therefore the units of measurement of milligrams and micrograms respectively were used as written above. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated methods of randomisation
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Machtinger 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 patient unaccounted, it is unclear from which study group they were lost
Selective reporting (reporting bias)	Unclear risk	No protocol or full text available but no obvious selective reporting
Other bias	Low risk	Mifepristone provided as a non-limited gift by A. Lapidot

Machtinger 2004

Study characteristics	
Methods	Single-centre, 4-arm, unblinded, randomised controlled trial
Participants	205 women attending a medical centre in Israel between unspecified dates with a miscarriage of < 9 weeks gestation (missed miscarriage only)
Interventions	Mifepristone 600 milligrams given orally + misoprostol 400 micrograms given orally 48 hours later and if needed repeat of misoprostol dose 3 hours later versus mifepristone 600 milligrams given orally + misoprostol 800 micrograms given vaginally 48 hours later versus misoprostol 400 micrograms given orally + misoprostol 400 micrograms given orally 48 hours later and if needed repeat of misoprostol dose 3 hours later versus misoprostol 800 micrograms given vaginally + misoprostol 800 micrograms given vaginally 48 hours later all as an outpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complications; need for unplanned/emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; pyrexia
Notes	Abstract only, no corresponding author details, for purposes of this review, the two arms both containing mifepristone and misoprostol and the two arms both containing misoprostol only were combined. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated method of randomisation
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Machtinger 2004 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol or full text available but no obvious selective reporting
Other bias	Unclear risk	Group 2 > 50% smaller than Group 1, Mifepristone provided as a non limited gift by A. Lapidot.

Montesinos 2011

Study characteristics		
Methods	Multi-centre, 2-arm, unblinded, randomised controlled trial	
Participants	242 women attending a tertiary maternity hospital or a small private secondary level family planning clinic in Ecuador between 6th November 2006 and 28th November 2007 with a miscarriage of ≤ 12 weeks gestation (incomplete miscarriage only)	
Interventions	Misoprostol 600 micrograms given orally as an outpatient versus suction aspiration either as an outpatient or inpatient manual procedure	
Outcomes	Complete miscarriage; days of bleeding; women's views/satisfaction; nausea; vomiting; pyrexia	
Notes	Clinicaltrials.gov trial registration number NCT00674232. Source of funding not stated, declarations of interest not stated.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Remotely created, stratified, computer-generated random sequence in blocks of 10
Allocation concealment (selection bias)	Low risk	Remotely created, sequentially-numbered, sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	16% lost to follow-up
Selective reporting (reporting bias)	High risk	Secondary outcomes reported in paper were not pre-specified in the original protocol that was registered.
Other bias	Unclear risk	The method of outcome assessment varied between sites with some being assessed clinically and others using ultrasound, funded by Packard Foundation

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Moodliar 2005

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	94 women attending a tertiary university teaching hospital in South Africa between October 2003 and April 2004 with a miscarriage of ≤13 weeks gestation (incomplete miscarriage only)
Interventions	Misoprostol 600 micrograms given vaginally (as a single dose on day 1 and if needed on day 2) as an in-patient versus dilatation and curettage as an inpatient procedure
Outcomes	Complete miscarriage; need for unplanned/ emergency surgical procedure; pain scores; pelvic inflammatory disease, endometritis or sepsis; days of bleeding; women's views/ satisfaction; nausea; vomiting; diarrhoea
Notes	Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated patient number allocation
Allocation concealment (selection bias)	Low risk	Consecutively-numbered, sealed, envelopes created by a third party
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Muffley 2002

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	50 women attending a naval military medical centre in the USA between June 1999 and March 2000 with a miscarriage of < 12 weeks gestation (missed miscarriage only)
Interventions	Misoprostol 800 micrograms given vaginally (as a single dose on day 1 and if needed on day 2) as an outpatient versus suction aspiration either as an inpatient or an outpatient

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Muffley 2002 *(Continued)*

Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/ emergency surgical procedure; nausea; vomiting; diarrhoea
Notes	Source of funding not stated, declarations of interest not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation via computer-generated, random number table
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, sealed, opaque envelopes created by a third party
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Unclear risk	The study authors noted that some medical patients had misoprostol co-administered with a vaginal lubricant which could have introduced non-uniformity of dosing or a variable absorption pattern. Authors acknowledge this study maybe subject to a type 2 statistical error due to overestimation of the success of misoprostol.

Nadarajah 2014

Study characteristics

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	360 women attending a tertiary hospital in Malaysia between 1st January 2009 and 31st December 2009 with a miscarriage of ≤ 14 weeks gestation (both incomplete and missed miscarriage)
Interventions	Suction aspiration as an inpatient procedure versus expectant management as an outpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/ emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; mean volumes of blood loss; change in haemoglobin measurements before and after the miscarriage; days of bleeding; cervical tears; women's views/satisfaction; readmission to hospital
Notes	Source of funding not stated, declarations of interest not stated.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Nadarajah 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence prepared in blocks of 10
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded to the interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Nasreen 2009

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	216 women attending a university hospital in Bangladesh between January 2006 and January 2008 with a miscarriage of ≤10 weeks gestation (both incomplete and missed miscarriage)
Interventions	Misoprostol 400 micrograms given orally (every 4 hours for 3 doses in total) + if needed misoprostol 200 micrograms given orally 48 hours later versus suction aspiration with cervical priming using misoprostol 400 micrograms given orally as an outpatient manual procedure
Outcomes	Complete miscarriage; women's views/ satisfaction; pyrexia
Notes	Abstract only available, no corresponding author details. It is stated 216 women were randomised but only 100 in each arm. It is not explained what happened to these 16 patients. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Nasreen 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	16 patients not accounted for in each arm compared to initial randomisation
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Ngai 2001

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	60 women attending a university tertiary hospital in Hong Kong between 1998 and 1999 (exact dates not specified) with a miscarriage of ≤ 12 weeks gestation (both incomplete and missed miscarriage)
Interventions	Misoprostol 400 micrograms given vaginally (as a single dose on day 1 and if needed on day 3 and day 5) as an outpatient versus expectant management as an outpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; nausea; vomiting; diarrhoea
Notes	It is not stated in the paper what the type of infection was but it is the judgment of the authors the cases of infection would be of gynaecological origin or sepsis. Study was supported by the Committee on Research and Conference Grants, the University of Hong Kong; declarations of interest not stated.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Validated randomisation table
Allocation concealment (selection bias)	Low risk	Serially-labelled, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being expectant

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Ngai 2001 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Nielsen 1995

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	155 attending a university hospital in Sweden between December 1992 and March 1994 with a miscarriage of < 13 weeks gestation (incomplete miscarriage only)
Interventions	Expectant management as an outpatient versus dilatation and curettage as an inpatient in a 2:1 ratio
Outcomes	Complete miscarriage; pelvic inflammatory disease, endometritis or sepsis; days of bleeding
Notes	Supported by grants from the Swedish Medical Research Council (B95-17X-11237-01A); declarations of interest not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation via drawing pre-prepared sealed envelopes
Allocation concealment (selection bias)	Low risk	Allocation via drawing sealed envelopes from a box
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being surgical and other being expectant
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Nielsen 1995 *(Continued)*

Other bias	Low risk	No other sources of bias noted

Nielsen 1999

Study characteristics		
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial	
Participants	122 women attending a university hospital in Sweden between unspecified dates with a miscarriage of < 13 weeks gestation (incomplete miscarriage only)	
Interventions	Mifepristone 400milligrams given orally + misoprostol 400 micrograms given orally 48 hours later as an outpatient versus expectant management as an outpatient	
Outcomes	Complete miscarriage; need for unplanned/ emergency surgical procedure; pain score; pelvic inflammatory disease, endometritis or sepsis; days of bleeding; women's views/ satisfaction	
Notes	Source of funding not stated, declarations of interest not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being expectant
Blinding of outcome assessment (detection bias) All outcomes	High risk	It is stated the study was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Niinimaki 2006

Study characteristics		
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial	

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Niinimaki 2006 *(Continued)*

Participants	98 women attending a university hospital in Finland between 4th February 2003 and 8th December 2004 with a miscarriage in the first trimester (exact gestation unspecified) (both incomplete and missed miscarriage)
Interventions	Mifepristone 200 milligrams given orally + misoprostol 800 micrograms given vaginally 24 to 72 hours later as an outpatient versus suction aspiration as an inpatient procedure
Outcomes	Complete miscarriage; need for unplanned/ emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; women's views/ satisfaction; re-admission to hospital
Notes	Some of the surgical arm may have received cervical priming with 400 micrograms of misoprostol given vaginally, however, it is the judgment of the authors the majority would not have been, as cervical priming was mainly given to nulliparous patients and the mean parity of the surgical arm was 1.7. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Third party, computer randomisation was used in blocks of 6
Allocation concealment (selection bias)	Low risk	Numbered, opaque, envelopes created by a third party
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Nwafor 2020

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	100 women attending a university hospital in Nigeria between February 2018 and August 2018 with a miscarriage of <13 weeks of gestation (incomplete miscarriage only)
Interventions	Misoprostol 600 micrograms given orally as an outpatient versus manual vacuum aspiration as an inpatient

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Nwafor 2020 *(Continued)*

Outcomes	Complete miscarriage, need for emergency surgery, infection, cervical tear
Notes	No external funding obtained to conduct the study, authors declare no conflicts of interest.; no evidence of prospective trial registration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A statistician blinded to the study's objectives generated the allocation sequence by simple randomisation using `computer-generated` random numbers.
Allocation concealment (selection bias)	Low risk	The allocation concealment was achieved by placing the allocation in sequentially numbered, opaque, sealed identical envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical management
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors not blinded to the intervention allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% of women lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No registered protocol or prospective trial registration available
Other bias	Low risk	No other sources of bias noted

Patua 2013

Study characteristics

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	100 women attending a university hospital in India in 2009 (exact dates unspecified), with a miscarriage of ≤ 12 weeks gestation (incomplete miscarriage only)
Interventions	Misoprostol 400 micrograms given vaginally (every 3 hours for 3 doses in total) as an inpatient versus suction aspiration as an inpatient
Outcomes	Complete miscarriage; need for unplanned/ emergency surgical procedure; change in haemoglobin measurements before and after the miscarriage; pyrexia
Notes	Source of funding not stated, the authors declare no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Patua 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Random number table used for randomisation
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Pereira 2006

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	100 women attending a University hospital in Brasil between 1st January 2003 and 17th March 2004, with a miscarriage of <13 weeks gestation (incomplete miscarriage only)
Interventions	Dilatation and curettage as an inpatient versus suction aspiration as an outpatient manual procedure
Outcomes	Composite outcome of death or serious complications; change in haemoglobin measurement before and after the miscarriage; cervical tear; mean duration of hospital stay; pyrexia
Notes	Paper available in Portuguese only. Translation used for data extraction. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated how random sequence was achieved
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm using general anaesthesia and other not using anaesthetic

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Pereira 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available, figures reported in results text not reported
Other bias	Low risk	No other sources of bias noted

Phusaanantakul 2010

Study characteristics		
Methods	Single-centre, 2-arm, double-blinded, placebo-controlled randomised trial	
Participants	48 women attending a university hospital in Thailand between October 2008 and June 2009 with a miscarriage of < 12 weeks gestation (missed miscarriage only)	
Interventions	Isosorbide mononitrate 20 milligrams given vaginally 4 hours before suction aspiration as an inpatient versus placebo given vaginally 4 hours before suction aspiration as an inpatient	
Outcomes	Women's views/ satisfaction	
Notes	Source of funding not stated, the authors declare no conflicts of interest.	
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	Sequentially-numbered, sealed, opaque envelopes used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double blinded, placebo was identical-looking to intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention versus placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	High risk	No protocol available and no results given for outcomes such as nausea, vomiting, headache, palpitations and vaginal bleeding which were discussed in the materials and methods section

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Phusaanantakul 2010 *(Continued)*

Other bias	Low risk	No other sources of bias noted

Sahin 2001

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	80 women attending a university hospital in Turkey between unspecified dates, with a miscarriage of ≤ 10 weeks gestation (incomplete miscarriage only)
Interventions	Misoprostol 200 micrograms given vaginally + misoprostol 200 micrograms given via an unspecified route 4-6 hourly for 5 days as an outpatient versus suction aspiration as either an inpatient or outpatient procedure
Outcomes	Complete miscarriage; pelvic inflammatory disease, endometritis or sepsis; change in haemoglobin measurement before and after the miscarriage; days of bleeding; women's views/ satisfaction
Notes	Source of funding not stated, declarations of interest not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation process not stated
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Salam 2016

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Salam 2016 *(Continued)*

Participants	610 women attending a university hospital in Pakistan between July 2014 and July 2015 with a miscarriage of < 12 weeks gestation (incomplete miscarriage only)
Interventions	Suction aspiration as a outpatient manual procedure versus dilatation and curettage as an outpatient
Outcomes	Complete miscarriage
Notes	Source of funding not stated, declarations of interest not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not stated
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants or personnel not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available and no other outcomes available
Other bias	Low risk	No other sources of bias noted

Schreiber 2018

Study characteristics

Methods	Multi-centre, 2-arm, single-blinded, randomised controlled trial
Participants	300 women attending 2 university hospitals in the USA between May 2014 and April 2017, with a miscarriage of <13 weeks gestation (missed miscarriage only)
Interventions	Mifepristone 200 milligrams given orally + misoprostol 800 micrograms given vaginally 24 hours later (and if needed repeated 48 to 72 hours later) as an outpatient versus misoprostol 800 micrograms given vaginally (and if needed repeated 48 to 72 hours later) as an outpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complications; pelvic inflammatory disease, sepsis or endometritis; nausea, vomiting, diarrhoea, pyrexia

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Schreiber 2018 *(Continued)*

Notes	PreFaiR trial Clinicaltrials.gov NCT02012491. Funded by the National Institute of Child Health and Human Development. Dr. Creinin reports receiving consulting fees from Danco Laboratories. No other potential conflict of interest relevant to this article were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, blocked and stratified randomisation
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% lost to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes relevant to this review stated in protocol are reported
Other bias	Low risk	No other sources of bias noted

Schwarzler 2003

Study characteristics

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	104 women attending a university hospital in Austria between unspecified dates, with a miscarriage in the 1st trimester (exact gestation unspecified) (type of miscarriage unspecified)
Interventions	Dilatation and curettage as an inpatient procedure versus expectant management as an outpatient
Outcomes	Data presented in an unusable form
Notes	Abstract only, no corresponding author details available, data presented in an unusable form. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Schwarzler 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being expectant and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available. No contact details available.
Other bias	Low risk	No other sources of bias noted

Shaheen 2017

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	104 women attending a university hospital in Pakistan between January 2016 and June 2016, with a miscarriage of < 12 weeks gestation (missed miscarriage only)
Interventions	Suction aspiration as an outpatient manual procedure versus misoprostol 800 micrograms given vaginally (and misoprostol 400 micrograms given vaginally every 6 hours for 2 doses in total)
Outcomes	Complete miscarriage
Notes	Source of funding not stated, declarations of interest not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated how random sequence was achieved
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Shaheen 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available, only complete miscarriage outcome reported
Other bias	Low risk	No other sources of bias noted

Shaikh 2008

Study characteristics		
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial	
Participants	200 women attending a university hospital in Bangladesh between unspecified dates, with a miscarriage of <10 weeks gestation (both incomplete and missed miscarriage)	
Interventions	Misoprostol 400 micrograms given orally every 4 hours for 3 doses in total (and if needed entire regimen repeated) as an inpatient versus misoprostol 400 micrograms given orally + suction aspiration as an outpatient manual procedure	
Outcomes	Data presented in an unusable form	
Notes	Abstract only, no corresponding author details available, data presented in an unusable form. Source of funding not stated, declarations of interest not stated.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available. No contact details available.
Other bias	Low risk	No other sources of bias noted

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Shelley 2005

Study characteristics	
Methods	Multi-centre, 3-arm, unblinded, randomised controlled trial
Participants	27 women attending 3 district general hospitals, 1 tertiary hospital and 1 specialist women's hospital in Australia between June 1999 and December 2000 with a miscarriage of ≤ 13 weeks gestation (incomplete miscarriage only)
Interventions	Misoprostol 400 micrograms given vaginally (and repeated 4-6 hours later if needed) as an outpatient versus expectant management as an outpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/emergency surgical procedure; pelvic inflammatory disease, endometritis or sepsis; nausea; vomiting; diarrhoea
Notes	An additional surgical arm was reported, however, it was combined suction aspiration and dilatation and curettage and therefore data were not able to extracted separately, author contacted on 31-Mar-2019 but email address no longer in use, therefore surgical arm excluded for purposed of this review. VICMIST trial terminated early due to poor recruitment from eligible population.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Third-party, remote, stratified, computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Third-party, remote, computer-generated randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being expectant
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	Funding by Department of Human Services, Victoria, Best Practice Initiatives Grant and an MBF Medical Research Award.

Shuaib 2013

Study characteristics

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Shuaib 2013 *(Continued)*

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	107 women attending a district general hospital in Yemen between 1st December 2010 and 31st November 2011, with a miscarriage of ≤ 12 weeks (missed miscarriage only)
Interventions	Dilatation and curettage as an inpatient versus misoprostol 400 micrograms given vaginally (and misoprostol 200 micrograms given vaginally every 4 hours for 11 doses in total if needed) as an inpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complication; pelvic inflammatory disease, endometritis or sepsis; cervical tear; women's views/ satisfaction; re-admission to hospital
Notes	Source of funding not stated, declarations of interest not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not stated
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Shwekerela 2007

Study characteristics

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	300 women attending a tertiary hospital in Tanzania between July 2004 and April 2005 with a miscarriage of < 12 weeks gestation (incomplete miscarriage only)
Interventions	Misoprostol 600 micrograms given orally as an outpatient versus suction aspiration as an outpatient manual procedure
Outcomes	Complete miscarriage; pelvic inflammatory disease, endometritis or sepsis; pain scores; women's views/ satisfaction; nausea; vomiting; pyrexia

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Shwekerela 2007 *(Continued)*

Notes	Source of funding not stated, declarations of interest not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Third-party, remote, computer-generated, randomisation in blocks of 10
Allocation concealment (selection bias)	Low risk	Consecutively numbered, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol mentioned in text but not available for review, no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Sinha 2018

Study characteristics

Methods	Single-centre, 2-arm, double-blinded, randomised placebo-controlled trial
Participants	92 women attending a university hospital in India between October 2011 and April 2013 with a miscarriage of ≤12 weeks gestation (missed miscarriage only)
Interventions	Mifepristone 200mg given orally + misoprostol 800 micrograms given vaginally 48 hours later (and+ 4 hours later if needed misoprostol 400 micrograms given orally + 3 hours later if needed misoprostol 400 micrograms given orally and repeated every 3 hours for a maximum of 2 doses in women ≤9 weeks of gestation or 4 doses in women >9 weeks of gestation versus placebo given orally + misoprostol 800 micrograms given vaginally 48 hours later + 4 hours later if needed misoprostol 400 micrograms given orally + 3 hours later if needed misoprostol 400 micrograms given orally and repeated every 3 hours for a maximum of 2 doses in women ≤9 weeks of gestation or 4 doses in women >9 weeks of gestation
Outcomes	Complete miscarriage; composite outcome of death or serious complications; need for unplanned/emergency surgical procedure; change in haemoglobin measurements before and after the miscarriage; days of bleeding
Notes	Clinical Trial Registry of India (CTRI 2013/03/003492). Source of funding not stated, declarations of interest not stated.

Risk of bias

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Sinha 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Third-party, computer-generated, random number tables used
Allocation concealment (selection bias)	Low risk	Consecutively-numbered, sealed envelopes created by a third party used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Similar looking placebo and mifepristone tablets were used for blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Decoding of sealed envelopes only done at time of analysis and so outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% of patients lost to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes stated in trial registry were reported
Other bias	Low risk	No other sources of bias noted

Stockheim 2006

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	115 women a university tertiary hospital in Israel between July 2001 and December 2002 with a miscarriage of < 9 weeks gestation (missed miscarriage only)
Interventions	Mifepristone 600 milligrams given orally + misoprostol 400 micrograms given orally 48 hours later (and repeated 3 hours later if needed) as an outpatient versus misoprostol 400 micrograms given orally (and repeated 3 hours later if needed and repeated again for 2 further doses 48 hours later if needed) as an outpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complications; need for unplanned/emergency surgical procedure; pyrexia
Notes	Source of funding not stated, declarations of interest not stated

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	Sequentially-numbered, sealed, opaque envelopes used

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Stockheim 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants and personnel were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Tationo 2012

Study characteristics		
Methods	Single-centre, 2-arm, randomised controlled trial	
Participants	186 women attending a tertiary hospital in Malaysia between unspecified dates, with a miscarriage in the 1st trimester (exact gestation unspecified) (incomplete miscarriage only)	
Interventions	Suction aspiration as a manual procedure versus dilatation and curettage	
Outcomes	Data presented in an unusable form	
Notes	Abstract only, no corresponding author details available, data presented in an unusable form. Source of funding not stated, declarations of interest not stated.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated if participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias)	Low risk	No patients lost to follow-up

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Tationo 2012 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available. No contact details available.
Other bias	Low risk	No other sources of bias noted

Taylor 2011

Study characteristics		
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial	
Participants	230 women attending a tertiary hospital in Ghana between 16th June 2004 and 20th July 2005, with a miscarriage of < 12 weeks gestation (incomplete miscarriage only)	
Interventions	Misoprostol 600 micrograms given orally as an outpatient versus suction aspiration as an outpatient manual procedure	
Outcomes	Complete miscarriage; composite outcome of death or serious complications; need for unplanned/ emergency surgical procedure; pain score; days of bleeding; women's views/ satisfaction; nausea; vomiting; pyrexia	
Notes	Funding was provided by the Fred H. Bixby Foundation and the David and Lucile Packard Foundation. The authors declare no conflicts of interest.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Third-party, computer-generated randomisation in blocks of 10
Allocation concealment (selection bias)	Low risk	Consecutively-numbered, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol or full text available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Torre 2012

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	182 women attending a teaching hospital in France between April 2003 and April 2006, with a miscarriage of <14 weeks gestation (both incomplete and missed miscarriage)
Interventions	Mifepristone 200 milligrams given orally + misoprostol 400 micrograms given vaginally 48 hours later as an outpatient versus expectant management as an outpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complications; need for unplanned/emergency surgical procedure; pyrexia
Notes	Clinicaltrials.gov identifier NCT00190294 Expectant arm in trial was delayed mifepristone 200 milligrams given orally + 48 hours later misoprostol 400 micrograms given vaginally 7 days after randomisation. For purposes of this review data were extracted at day 7 before this arm received intervention but after expectant treatment was given for 7 days. Funding was provided by Assistance Publique Hôpitaux de Paris. The authors report no conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Third-party, computer-generated randomisation in blocks of 4
Allocation concealment (selection bias)	Low risk	Third-party, remote, computer-generated randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants or personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes listed in protocol have been reported
Other bias	Low risk	No other sources of bias noted

Trinder 2006

Study characteristics	
Methods	Multi-centre, 3-arm, unblinded, randomised controlled trial

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Trinder 2006 *(Continued)*

Participants	926 women attending 7 hospitals in the UK between May 1997 and December 2001, with a miscarriage of < 13 weeks gestation (both incomplete and missed miscarriage)
Interventions	Suction aspiration as an inpatient procedure versus expectant management as an outpatient versus mifepristone 200 milligrams given orally + misoprostol 800 micrograms given vaginally 24 to 48 hours later as an inpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complications; pelvic inflammatory disease, endometritis or sepsis
Notes	272 patients with incomplete miscarriage are not reported as part of this review as the medical arm would have included those treated with purely misoprostol and those given mifepristone before misoprostol. Therefore the data for incomplete miscarriage are excluded as it would have been contaminated. Funded by a South and West NHS Executive research and development grant. The MIST trial group accepted a donation of £20,000 from Exelgyn, the manufacturers of mifepristone, which is declared as a conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Third-party, remote randomisation
Allocation concealment (selection bias)	Low risk	Centralised, third-party, randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical, one arm being surgical and other being expectant
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Ulstrup 1997

Study characteristics

Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	An unspecified number of women attending a district general hospital in Denmark between unspecified dates, with a miscarriage <13 weeks of gestation (incomplete miscarriage only)
Interventions	Dilatation and curettage as an inpatient procedure versus expectant management as an outpatient

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Ulstrup 1997 *(Continued)*

Outcomes	Data presented in an unusable form
Notes	Abstract only, no corresponding author details available, data presented in an unusable form. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being expectant and other arm being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available or full text paper available. No contact details available.
Other bias	Low risk	No other sources of bias noted

Verkuyl 1993

Study characteristics

Methods	Single-centre, 2-arm, randomised-controlled trial (blinding not mentioned)
Participants	357 women attending a tertiary hospital in Zimbabwe between unspecified dates, with a miscarriage of ≤ 18 weeks gestation (incomplete miscarriage only)
Interventions	Suction aspiration as an outpatient procedure versus dilatation and curettage as an outpatient procedure
Outcomes	Complete miscarriage; composite outcome of death of serious complication; pelvic inflammatory disease, endometritis or sepsis; mean volumes of blood loss; change in haemoglobin measurements before and after the miscarriage; days of bleeding
Notes	It was noted the maximum gestation age of the study was 18 weeks, however, the mean gestational age in weeks of the suction aspiration arm was 8.7 with a standard deviation of 3.1 and the mean gestational age in weeks of the dilatation and curettage arm was 9.7 with a standard deviation of 3.1 and so it was felt that the vast majority of patients would have been ≤ 14 weeks gestation and therefore the paper was included. Source of funding not stated, declarations of interest not stated.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Verkuyl 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table was used
Allocation concealment (selection bias)	Low risk	Consecutively-numbered, sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	>20% lost to follow-up in both arms
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Weeks 2005

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	317 women attending a university hospital in Uganda between August 2001 and October 2002, with a miscarriage of < 13 weeks gestation (incomplete miscarriage only)
Interventions	Misoprostol 600 micrograms given orally as an outpatient versus suction aspiration as an outpatient manual procedure
Outcomes	Complete miscarriage; composite outcome of death or serious complications; pelvic inflammatory disease, endometritis or sepsis; cervical tear; women's views/ satisfaction; pyrexia
Notes	Source of funding not stated, declarations of interest not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers were used
Allocation concealment (selection bias)	Low risk	Consecutively-numbered, opaque, sealed envelopes

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Weeks 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	>30% lost to follow-up in both arms, >10% difference between arms in terms of numbers lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Wijesinghe 2011

Study characteristics	
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	140 women attending a university hospital in Sri Lanka between December 2007 and July 2009, with a miscarriage of < 14 weeks gestation (incomplete miscarriage only)
Interventions	Expectant management as an inpatient versus suction aspiration as an inpatient
Outcomes	Complete miscarriage by day 14 post intervention; composite outcome of death or serious complication; pelvic inflammatory disease, endometritis or sepsis; change in haemoglobin before and after the miscarriage; cervical tear; mean duration of hospital stay
Notes	Sri Lankan clinical trials registry identifier SLCTR/2008/012, Protocol was retrospectively registered. Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, random numbers were used
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being expectant and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Wijesinghe 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes stated in protocol have been reported
Other bias	Low risk	No other sources of bias noted

Wood 2002

Study characteristics	
Methods	Single-centre, 2-arm, double-blinded, placebo-controlled, randomised trial
Participants	50 women attending a university hospital in Canada between February 1999 and April 2000 with a miscarriage of ≤ 12 weeks gestation (missed miscarriage only)
Interventions	Misoprostol 800 micrograms given vaginally (and repeated 24 hours later if needed) as an outpatient versus placebo given vaginally (and repeated 24 hours later if needed) as an outpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/emergency surgical procedure; change in haemoglobin measurements before and after the miscarriage
Notes	Source of funding not stated, declarations of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation in blocks of between 4 and 8
Allocation concealment (selection bias)	Low risk	Numbered envelopes created by a third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Personnel were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Zhang 2005

Study characteristics	
Methods	Multi-centre, 2-arm, unblinded, randomised controlled trial
Participants	652 women attending 4 university medical centres in theUSA between March 2002 and March 2004, with a miscarriage of <13 weeks gestation (both incomplete and missed miscarriage)
Interventions	Misoprostol 800 micrograms given vaginally (as a single dose on day 1 and if needed day 3) as an outpatient versus suction aspiration either as an outpatient manual or inpatient electric procedure
Outcomes	Complete miscarriage; pain scores; pelvic inflammatory disease, endometritis or sepsis; change in haemoglobin measurements before and after the miscarriage; nausea; vomiting; diarrhoea; pyrexia
Notes	Funded by contracts (N01-HD-1-3321, N01-HD-3322, N01-HD3323, N01-HD-3324, and N01-HD-3325) with the National Institute of Child Health and Human Development, National Institutes of Health. Drs. Creinin and Westhoff report having served as consultants to Pfizer, which now owns Searle. Dr. Westhoff reports having received grant support from Pfizer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised, computer-generated randomisation in a 3:1 randomisation
Allocation concealment (selection bias)	Low risk	Centralised, computer-automated, telephone response system,
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to one arm being medical and other being surgical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available but no evidence of selective reporting
Other bias	Low risk	No other sources of bias noted

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbasalizadeh 2018	Wrong intervention - letrozole + misoprostol versus misoprostol
Abdel Fattah 1997	Wrong patient population - women with a 2nd trimester miscarriage and intrauterine fetal death

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Abd-El-Maeboud 2012	Wrong patient population - women with a pregnancy of 14-26 weeks of gestation
Abdelshafy 2019a	Wrong intervention - comparator is same as intervention, vaginal misoprostol versus sublingual misoprostol
Abediasl 2016	Wrong patient population - women with a 2nd trimester miscarriage and intrauterine fetal death
Abeysundara 2012	Wrong study design - qualitative work on patient perceptions
Ajand 2017	Wrong intervention - comparator is same as intervention, vaginal misoprostol versus sublingual misoprostol
Al 2003	Wrong intervention - misoprostol versus dinoprostone
Al-Bdour 2007	Wrong patient population - women with a missed miscarriage between 9 and 22 weeks gestation. Unable to extract data for women with a miscarriage < 14 weeks gestation.
Ali 2015	Wrong intervention - misoprostol + isosorbide mononitrate versus misoprostol + placebo
Ali 2017	Wrong intervention - comparator is same as intervention, outpatient extended low dose buccal misoprostol versus inpatient standard dose vaginal misoprostol
Allameh 2020	Ineligible interventions for this review
Almog 2005	Wrong patient population - women undergoing mid-trimester terminations
Altaf 2006	Wrong patient population - women undergoing termination of pregnancy from 10 to 28 weeks of gestation
Ameen 2009	Trial compared different routes of administration of the same treatment, which are excluded from this review
Amjad 1999	Wrong patient population - women with a miscarriage greater than 14 weeks of gestation
Anderman 2000	Wrong patient population - women with a mid-trimester miscarriage
Anderson 2009	Wrong intervention - Comparator is same as intervention, oral mifepristone + oral misoprostol versus oral mifepristone + vaginal misoprostol
Aramide 2014	Ineligible interventions for this review
Arteaga-Troncoso 2005	Wrong interventions - each arm has been combined for different types of surgical management and therefore contains patients who have had either sharp curettage or suction curettage. It is not possible to extract data for each intervention separately within each arm.
Autry 1999	Wrong intervention - misoprostol versus intramuscular methotrexate + misoprostol
Avila-Vergara 1997	Wrong patient population - women with fetal death undergoing induction of labour (exact gestations not stated)
Avila VergaraMa 1997	Wrong patient population - women with intrauterine fetal death of 20 weeks of gestation or more
Aye 2017	Wrong intervention - comparator is same as intervention, vaginal misoprostol versus sublingual misoprostol

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Ayudhaya 2006	Wrong intervention - comparator is same as intervention, oral misoprostol versus sublingual misoprostol
Azra 2007	Wrong patient population - women having second trimester terminations
Bagratee 2009	Abstract only, numbers reported in each group not provided and no corresponding author details
Bani-Irshaid 2006	Wrong patient population - women having second trimester and early third trimester terminations
Barnhart 2004	Ineligible intervention for this review
Bartz 2013	Wrong intervention - comparator is same as intervention, buccal misoprostol + suction curettage versus osmotic dilator + suction curettage
Bebbington 2002	Wrong patient population - women having mid-trimester terminations
Behrashi 2008	Wrong patient population - women having second trimester terminations
Ben-Meir 2009	Wrong patient population - women having terminations between 14 and 25 weeks of gestation
Betstadt 2008	Trial registration document only. Author emailed who confirmed study was terminated and no data published. Original data no longer available
Biswas 2007	Wrong patient population - women having terminations between 13 and 20 weeks of gestation
Blanchard 2004	Wrong intervention - comparator is same as intervention, 600 mcg misoprostol versus 2 x doses of 600 mcg misoprostol
Blohm 1997	Wrong study design - questionnaire based qualitative study
Bracken 2014	Wrong patient population - women with intrauterine fetal death between 14 and 28 weeks of gestation
Bracken 2019	Conference abstract only and does not state gestational age of participants. No author contact details available
Brouns 2010	Wrong patient population - women with intrauterine fetal death between 14 and 24 weeks of gestation
Cabrol 1990	Wrong patient population - women with intrauterine fetal death after 16 weeks of gestation
Caliskan 2005	Wrong patient population - women with a miscarriage between 13 and 20 weeks of gestation
Caliskan 2009	Wrong patient population - women with a miscarriage between 15 and 22 weeks of gestation
Chen 2008a	Wrong intervention - cervical priming before dilatation plus curettage
Chittacharoen 2003	Wrong patient population - women with intrauterine fetal death between 16 and 41 weeks of gestation
Chowdhury 2012	Wrong patient population - women with a second trimester miscarriage
Cleeve 2016	Wrong intervention - physician administration of misoprostol versus midwife administration of misoprostol

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Clevin 2001	Wrong intervention - gemeprost versus dilatation and curettage
Creinin 1997	Wrong intervention - comparator is same as intervention, oral misoprostol versus vaginal misoprostol
Creinin 2004	Wrong study design - not randomised
Cruz 2017	Trial compared different methods of administration of the same treatment, which are excluded from this review.
Danielsson 2012	Wrong intervention - comparator is same as intervention, misoprostol 800 mcg given vaginally versus misoprostol 800 mcg given vaginally with repeated doses of misoprostol 400 mcg given orally 3, 5, 7 and 9 hours later
David 2003	Ineligible intervention for this review
David 2005	Ineligible intervention for this review
Davis 2004	Wrong study design - not randomised
Dee 2009	Wrong intervention - comparator is same as intervention, intrauterine misoprostol versus vaginal misoprostol
Dehbashi 2016	Wrong intervention - comparator is same as intervention, sublingual misoprostol versus vaginal misoprostol
Devall 2019	Wrong Intervention - feasibility study for the use of ultrasonography during surgical evacuation
Dhillon 2015	Wrong intervention - comparator is same as intervention, isosorbide mononitrate + suction curettage versus misoprostol + suction curettage
Dickinson 1998	Wrong patient population - women with intrauterine fetal death between 14 and 28 weeks of gestation
Dickinson 2002	Wrong patient population - women having a termination between 14 and 30 weeks of gestation
Dickinson 2003	Wrong patient population - women having a termination between 14 and 26 weeks of gestation
Diop 2009	Wrong intervention - comparator is same as intervention, sublingual misoprostol versus oral misoprostol
Dunford 2012	Study terminated 23rd August 2019 due to a lack of funding/ staff/facilities
Dunn 2008	Ineligible intervention for this review
Egarter 1995	Wrong intervention - gemeprostol versus dilatation and curettage
Elami-Suzin 2013	Wrong patient population - women either having a termination or with a missed miscarriage between 14 and 24 weeks of gestation
Elbareg 2018	Wrong intervention - letrozole + misoprostol versus misoprostol
Elhassan 2008	Wrong patient population - women with intrauterine fetal death between 13 and 28 weeks of gestation

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
El Sokkary 2016	Wrong intervention - comparator is same as intervention, sublingual misoprostol versus vaginal misoprostol
Eng 1997	Wrong patient population - women with intrauterine fetal death between 13 and 26 weeks of gestation
Eppel 2005	Wrong patient population - women having a termination between 13 and 23 weeks of gestation
Eslamian 2007	Wrong patient population - women having a termination between 14 and 24 weeks of gestation
EUCTR2011-001505-26-SE	Wrong intervention - comparator is same as intervention, repeated doses of vaginal misoprostol versus repeated doses of vaginal misoprostol of a difference dose
Ezzatosadat 2012	Wrong intervention - hyoscine + misoprostol versus placebo + misoprostol
Facchinetti 2001	Ineligible intervention for this review
Fadalla 2004	Wrong patient population - women with intrauterine fetal death between 13 and 28 weeks of gestation
Farooq 2018	Wrong study design - outcomes not reported separately for missed miscarriage which received cervical priming versus incomplete miscarriage which did not before vacuum aspiration, therefore data useful for this review cannot be extracted
Faxelid 2012	Wrong intervention - physician administration of misoprostol versus midwife administration of misoprostol
Feldman 2003	Wrong patient population - women having a termination between 14 and 23 weeks of gestation
Fiala 2005	Wrong patient population - women having a termination between 13 and 22 weeks of gestation
Firouzabadi 2012	Wrong intervention - Laminaria tents + suction dilatation and curettage versus misoprostol + suction dilatation and curettage
Freeman 2016	Wrong patient population - women between 14 and 24 weeks of gestation having either a termination or treatment of miscarriage
Ghorab 1998	Wrong patient population - women between 16 and 24 weeks of gestation having either a termination or treatment for intrauterine fetal death
Gilles 2004	Wrong intervention - comparator is same as intervention, vaginal misoprostol mixed with normal saline versus vaginal misoprostol
Gonzalez 2001	Wrong patient population - women between 12 and 28 weeks of gestation having either a termination or treatment for intrauterine fetal death
Graziosi 2005	Wrong study design - this is a letter to an editor about a telephone survey about fertility outcomes
Grimes 2005	Wrong patient population - women having a termination between 14 and 19 weeks of gestation
Gronlund 2002	Wrong study design - cross-over study
Guix 2005	Wrong patient population - women having a termination between 13 and 22 weeks of gestation
Halimi 2004	Wrong patient population - women between 14 and 28 weeks of gestation having either a termination or treatment for intrauterine fetal death

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Harrington 2004	Wrong intervention - transcervical amniotic puncture + misoprostol versus misoprostol
Hassan 2007	Wrong intervention - comparator is same as intervention, oral misoprostol versus rectal misoprostol
Hausler 1997	Wrong outcomes - HCG clearance tine, endometrial thickness, secondary bleeding. Original paper in German, full literal translation used.
Heard 2002	Wrong intervention - comparator is same as intervention, 400 mcg misoprostol versus 800 mcg misoprostol
Henshaw 1995	Wrong trial design - only party randomised. Abstract only available. No corresponding author details. Randomised data not able to be extracted.
Herabutya 1997	Wrong patient population - women with an intrauterine fetal death between 14 and 39 weeks of gestation
Herabutya 1997a	Wrong intervention - both arms are treated with suction curettage and sharp curettage after cervical priming. Not possible to separate out data needed for this review as suction curettage and dilatation and sharp curettage are two separate interventions in this review.
Herabutya 2005	Wrong patient population - women having a termination between 14 and 26 weeks of gestation
Herman 2017	Trial compared different routes of administration of the same treatment, which are excluded from this review.
Hernandez-Valencia 2003	Wrong intervention - comparison is ambulatory versus inpatient care
Hidalgo 2010	Ineligible intervention for this review
Hidar 2001	Wrong patient population - women having a termination between 13 and 29 weeks of gestation
Hidar 2005	Wrong patient population - women having a termination between 13 and 29 weeks of gestation
Hill 1991	Wrong patient population - women with an intrauterine fetal death in the second or third trimester
Hinshaw 1995	Wrong study design - only partly randomised. Abstract only available, no corresponding author details, unclear from abstract what exact nature of intervention is, whole data set not from only randomised patients, not able to extract data that is just from randomised patients
Hogg 2000	Wrong patient population - women having a termination between 16 and 24 weeks of gestation
Hombalegowda 2015	Wrong intervention - comparator is same as intervention, 400 mcg misoprostol versus 800 mcg misoprostol
Hooker 2016	Wrong intervention - application of hyalobarrier gel after dilatation and curettage for miscarriage
Huchon 2015	Wrong intervention - operative hysteroscopy versus suction aspiration
Hughes 1996	Non-randomised trial of treatment cost-effectiveness
Ibrahim 2019	Ineligible intervention for this review
Imran 2010	Wrong patient population - women between 14 and 28 weeks of gestation having either a termination or treatment for intrauterine fetal death

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
IRCT2015112421506N3 2016	Wrong intervention - Isonicotinic acid hydrazide + misoprostol versus misoprostol
IRCT2016122729062N1 2016	Wrong intervention - *Sesamum indicum* + misoprostol versus misoprostol
Islam 2006	Wrong patient population - women in the second trimester having either a termination or treatment for intrauterine fetal death
Jabir 2009a	Wrong intervention - comparator is same as intervention, oral misoprostol + surgery versus vaginal misoprostol + surgery versus oral placebo + surgery versus vaginal placebo + surgery. Surgery undefined and contact details no longer in use.
Jain 1994	Wrong patient population - women between 12 and 22 weeks of gestation having either a termination or treatment for intrauterine fetal death
Jain 1996	Wrong patient population - women between 12 and 22 weeks of gestation having either a termination or treatment for intrauterine fetal death
Jain 1999	Wrong patient population - women between 12 and 22 weeks of gestation having either a termination or treatment for intrauterine fetal death
Jamilian 2014	Wrong intervention - castor oil + misoprostol versus misoprostol
Javadi 2015	Wrong intervention - misoprostol versus letrozole + misoprostol
Johnson 1997	Wrong intervention - mifepristone + gemeprostol versus dilatation and curettage
Kakinuma 2020	Retrospective cohort study comparing treatment regimens administered between defined date ranges
Kamal 2005	Wrong patient population - women having a termination between 13 and 28 weeks of gestation
Kanhai 1988	Wrong patient population - women with intrauterine fetal death between 14 and 42 weeks of gestation
Kanhai 1989	Wrong patient population - women with intrauterine fetal death between 14 and 42 weeks of gestation
Kapp 2007	Wrong patient population - women in the second trimester having a termination
Kara 1999	Wrong patient population - women in the second trimester having treatment for intrauterine fetal death
Khanam 2019	Trial compares different dosages of the same treatment, which are excluded from this review
Khoosideh 2017	Ineligible intervention for this review
Khosravi 2017	Wrong patient population - women less than 14 weeks gestation having a termination of pregnancy
Klingberg-Allvin 2015	Wrong intervention - clinical assessment by a physician versus a midwife
Kovavisarach 2005	Wrong intervention - comparator is same as intervention, 600 mcg misoprostol versus 800 mcg misoprostol
Kurshid 2010	Wrong patient population - women having a termination between 19 and 23 weeks of gestation

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Kushwah 2009	Wrong intervention - comparator is same as intervention, mifepristone + sublingual misoprostol versus mifepristone + oral misoprostol
Lei 2015	Wrong intervention - mifepristone + misoprostol versus ultrasound guided surgical curettage
Lelaidier 1993	Wrong intervention - mifepristone versus placebo
Lemmers 2016	Wrong patient population - women having treatment for miscarriage after failed medical management of miscarriage with misoprostol
Leung 2004	Wrong patient population - women having treatment for miscarriage after failed medical management of miscarriage with misoprostol
Li 2018	Ineligible intervention for this review
Linn 2015	Wrong patient population - women with intrauterine fetal death greater than or including 20 weeks of gestation
Lippert 1978	Wrong patient population - women with intrauterine fetal death between 18 and 32 weeks of gestation
Louey 2000	This is a trial registration document. Email address listed no longer in use. No resulting published papers or data found.
Lu 2014	Wrong intervention - comparator is same as intervention, mifepristone + vaginal misoprostol versus mifepristone + oral misoprostol
Lughmani 2007	Wrong intervention - misoprostol versus PGE2
Mahjabeen, 2009	Wrong patient population - women in the second trimester having a termination of pregnancy
Makenzius 2017	Wrong intervention - physician administration of misoprostol versus midwife administration of misoprostol
Makhlouf 2003	Wrong patient population - women having a termination of pregnancy between 13 and 28 weeks of gestation
Marfou 2012	Ineligible intervention for this review
Martin 1955	Wrong patient population - majority of cases were greater than 28 weeks of gestation
Marwah 2016	Wrong intervention - comparator is same as intervention, vaginal misoprostol versus oral misoprostol
Mitwaly 2016	Wrong patient population - women with intrauterine fetal death between 13 and 24 weeks of gestation
Mizrachi 2017	Wrong intervention - comparator is same as intervention, 800 mcg misoprostol versus 2 x doses of 800 mcg misoprostol
Moran 2005	Wrong patient population - women with a pregnancy of unknown location
Mostafa-Gharebaghi 2010	Wrong patient population - includes women having a termination of pregnancy under 20 weeks of gestation. Data for women not having a termination and under 14 weeks of gestation not able to be extracted.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Mulayim 2009	Wrong patient population - includes women having a termination of pregnancy. Data for women with a miscarriage not presented separately.
Nakintu 2001	Wrong patient population - women with intrauterine fetal death above 18 weeks of gestation
Nasrollahi 2008	Wrong intervention - PGE2 (dinoprostone) administered intravenously versus intramuscularly in the management of missed miscarriage
Nassar 2005	Wrong patient population - women with intrauterine fetal death between 14 and 24 weeks of gestation
Nauman 2016	Wrong intervention - comparator is same as intervention, electric suction curettage versus manual suction curettage
NCT00426491 2007	Wrong intervention - letrozole + misoprostol versus placebo + misoprostol
NCT00670761 2008	Wrong study design - not randomised
NCT00797693 2008	Trial compared different routes of administration of the same treatment, which are excluded from this review.
NCT02141555 2014	Wrong intervention - comparator is same as intervention, vaginal misoprostol versus buccal misoprostol
NCT02342002 2015	Study terminated due to lack of funding. No contact details on trial registry.
NCT02580175 2015	Wrong intervention - blinded suction evacuation versus ultrasound guided suction evacuation
NCT02957305 2016	Trial compares different dosages of the same treatment, which are excluded from this review.
NCT03148314 2017	Wrong interventions - misoprostol in a low dose given sublingually or buccally as outpatient versus misoprostol at a standard dose as an inpatient
NCT03148561 2017	Wrong patient population - women having treatment for miscarriage after failed medical management of miscarriage with misoprostol
NCT03230825 2017	Wrong patient population - includes women having a termination of pregnancy in the first trimester
NCT03628625 2018	Wrong intervention - letrozole + misoprostol versus placebo + misoprostol
Ng 2015	Wrong intervention - inpatient versus outpatient misoprostol treatment
Ngoc 2004	Wrong comparator - both arms are misoprostol
Nguyen 2005	Wrong intervention - comparator is same as intervention, 600 mcg misoprostol versus 2 x doses of 600 mcg misoprostol
Niederauer 2018	Trial compares different dosages of the same treatment, which are excluded from this review.
Niromanesh 2005	Wrong patient population - women with intrauterine fetal death between 14 and 25 weeks of gestation
Nor 2006	Wrong patient population - women having a termination of pregnancy between 14 and 26 weeks of gestation

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Nuthalapaty 2005	Wrong patient population - women having a termination of pregnancy between 14 and 24 weeks of gestation
Nuutila 1997	Wrong patient population - women having a termination of pregnancy between 12 and 24 weeks of gestation
Ogden 2004	Wrong study design - qualitative study protocol
Owen 1999	Wrong patient population - women between 16 and 24 weeks of gestation having either a termination of pregnancy or treatment for intrauterine fetal death
Pang 2001	Wrong intervention - comparator is same as intervention, vaginal misoprostol versus oral misoprostol
Pansky 2011	Wrong intervention - women having their uterine cavity filled with Oxiplex/ AP gel versus no intervention after blunt hysteroscopic dissection for suspected retained products of conception
Paraskevaides 1992	Wrong intervention - dilatation and curettage versus prostaglandin F2 alpha versus trilostane
Paritakul 2010	Wrong intervention - comparator is same as intervention, sublingual misoprostol versus oral misoprostol
Perry 1999	Wrong patient population - women having a termination of pregnancy between 17 and 24 weeks of gestation
Petersen 2013	Wrong intervention - comparator is same as intervention, 400 mcg misoprostol versus 800 mcg misoprostol
Phupong 2004	Wrong patient population - women with a miscarriage < 20 weeks of gestation. Data for women with < 14 weeks gestation not analysed separately to >14 weeks gestation.
Piotrowski 1979	Wrong intervention - pretreatment with indomethacin versus no pretreatment before intravenous PGE2 (dinoprostone) for treatment of intrauterine fetal death
Pomeranz 2016	Wrong patient population - women having treatment for miscarriage after failed medical management of miscarriage with misoprostol
Pongsatha 2004	Wrong patient population - women having a termination of pregnancy between 14 and 28 weeks of gestation
Prasartsakulchai 2004	Wrong intervention - comparator is same as intervention, 400 mcg misoprostol versus 800 mcg misoprostol
Promwangkwa 2017	Wrong patient population - women having a termination of pregnancy in the 2nd trimester
Ragusa 1994	Ineligible intervention for this review
Rahimi-Sharbaf 2015	Wrong patient population - women having a termination of pregnancy between 13 and 24 weeks of gestation
Ramsey 2004	Wrong patient population - women in the second trimester having a termination of pregnancy
Rita 2006	Wrong intervention - comparator is same as intervention, oral misoprostol versus vaginal misoprostol

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Rivero-Lopez 1998	Wrong intervention - comparator is same as intervention, misoprostol + suction curettage versus laminaria stems + suction curettage
Robledo 2007	Wrong study design - not randomised
Roy 2003	Wrong patient population - women in the second trimester having a termination of pregnancy
Ruangchainikhom 2006	Wrong patient population - women having a termination of pregnancy less than 20 weeks of gestation
Saciloto 2011	Wrong study design - not randomised
Saeed 2018	Wrong intervention - comparator is same as intervention, oral misoprostol versus vaginal misoprostol
Saichua 2009	Wrong intervention - comparator is same as intervention, sublingual powered misoprostol versus sublingual tablet misoprostol
Salamalekis 1990	Wrong patient population - women with an intrauterine fetal death in the second trimester Wrong intervention - Prostaglandin F2 Alpha versus prostaglandin E2 (dinoprostone)
Sewzie 2014	Wrong intervention - comparator is same as intervention, sublingual misoprostol versus vaginal misoprostol versus oral misoprostol
Shaamash 2019	Trial compares different dosages of the same treatment, which are excluded from this review.
Shah 2010	Wrong intervention - comparator is same as intervention, sublingual misoprostol versus vaginal misoprostol
Sharifzadeh 2015	Ineligible intervention for this review
Shobeira 2007	Wrong patient population - women in the second trimester having a termination
Shochet 2012	Wrong intervention - misoprostol versus surgical evacuation (which includes both suction curettage and dilatation and curettage), corresponding author emailed to see if breakdown of data available but no response received
Shokry 2009	Wrong intervention - surgical evacuation followed by either misoprostol versus no misoprostol
Sonsanoh 2014	Wrong intervention - comparator is same as intervention, sublingual misoprostol versus vaginal misoprostol
Souizi 2020	Trial compares different dosages of the same treatment, which are excluded from this review
Srikhao 2005	Wrong intervention - comparator is same as intervention, 400 mcg misoprostol versus 800 mcg misoprostol
Sripramote 2000	Wrong intervention - cervical priming + dilatation and curettage
Su 2005	Wrong patient population - women having a termination of pregnancy between 12 and 24 weeks of gestation
Suchonwanit 1999	Wrong intervention - comparator is same as intervention, 200 mcg misoprostol versus 400 mcg misoprostol

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Surita 1997	Wrong patient population - Women with intrauterine fetal death greater than 15 weeks of gestation
Sweed 2015	Wrong intervention - placebo + misoprostol versus letrozole + misoprostol
Sweed 2018	Wrong intervention - misoprostol single dose versus misoprostol repeated doses
Tam 2002	Wrong study design - non interventional follow-up study to previous randomised trial
Tam 2005	Wrong study design - qualitative telephone interviews after previous randomised trial
Tan 1969	Wrong study design - case series
Tang 2003	Wrong intervention - comparator is same as intervention, sublingual misoprostol versus vaginal misoprostol
Tang 2006	Wrong intervention -cComparator is same as intervention, misoprostol for 3 doses versus misoprostol for 3 doses + misoprostol once a day for seven further days
Tanha 2010	Wrong patient population - women in the second trimester having a termination
Tanha 2010a	Wrong intervention - comparator is same as intervention, sublingual misoprostol versus vaginal misoprostol
Tanha 2013	Wrong patient population - women having a termination between 13 and 24 weeks of gestation
Tasnim 2011	Wrong intervention - comparator is same as intervention, electric suction curettage versus manual suction curettage
Tasnim 2014	Wrong intervention - inpatient versus outpatient suction curettage treatment
Teymouri 2017	Wrong intervention - misoprostol versus misoprostol + oestrogen valerate
Thavarasah 1986	Wrong intervention - Prostaglandin F2 alpha administered either intravenously, extramniotic or intramuscularly
Thida 2015	Wrong intervention - comparator is same as intervention, sublingual misoprostol versus vaginal misoprostol versus oral misoprostol
Thong 2005	Insufficient information to determine whether the trial data should be included in the review, and there are no corresponding author contact details.
Toppozada 1994	Wrong patient population - women with intrauterine fetal death greater than 20 weeks of gestation
Toptas 2011	Wrong patient population - women between 13 and 26 weeks of gestation having either a termination or treatment for intrauterine fetal death
Torky 2018	Wrong intervention - placebo + misoprostol versus letrozole + misoprostol
Vafaei 2019	Wrong intervention - herbal medicine myrrh versus expectant management
Van Mensel 2009	Wrong patient population - women with intrauterine fetal death between 14 and 42 weeks of gestation
Wieringa-de 2002	Wrong patient population - women having treatment for a miscarriage <16 weeks of gestation. Data of patients between 14-16 weeks of gestation unable to be extracted and 23.4% of patients in the expectant group and 31% of patients in the curettage group were between 12 and 16 weeks so

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
	it was the judgement of the authors that there would be too much contamination by patients >14 weeks of gestation to be included.
Wijesinghe 2012	Wrong study design - qualitative interviews on patient perceptions of expectant management of miscarriage
Yapar 1996	Wrong patient population - women having a termination between 14 and 28 weeks of gestation
Yilmaz 2005	Wrong patient population - women in the second trimester having either a termination of pregnancy or treatment for intrauterine fetal death
Yilmaz 2007	Wrong patient population - women in the second trimester having either a termination or treatment for intrauterine fetal death
Zanganeh 2010	Wrong patient population - women having a termination in the second trimester
Zhang 2000	Wrong patient population - women having a termination between 16 and 24 weeks of gestation

Characteristics of studies awaiting classification *[ordered by study ID]*

Fang 2009

Methods	Single-centre, 3-arm, unblinded, randomised controlled trial
Participants	90 women attending a university hospital in China between 1st September 2005 and 28th February 2007, with a miscarriage of ≤12 weeks gestation (missed miscarriage only)
Interventions	Misoprostol 400 micrograms given vaginally + suction aspiration (not stated if manual or electric) as an inpatient procedure versus misoprostol 400 micrograms given vaginally + repeated every 3 hours for 5 doses if needed as an inpatient versus mifepristone 200 mg given orally + misoprostol 400 micrograms given vaginally every 3 hours for 5 doses if needed 36-48 hours later as an inpatient
Outcomes	Complete miscarriage; need for unplanned/ emergency surgical procedure; women's views/ satisfaction
Notes	Awaiting clarification from authors re outcome data. Authors last contacted on 17-Feb-2021.

HCG: human chorionic gonadotropin; mcg: microgram; **PGE2:** prostaglandin E2.

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR1900023198 2019

Study name	The incidence of intrauterine adhesion after ultrasound-guided manual vacuum aspiration (USG-MVA): A prospective randomized controlled trial
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	1. Women 18 years old or above; 2. Women with miscarriage who are suitable candidates for USG-MVA; 3. first-trimester delayed miscarriage≤ 10 weeks of gestation; 4. incomplete miscarriage With POG ≤ 5cm; 5. haemodynamically stable; 6. tolerates well with speculum examination.
Interventions	Ultrasound guided manual vacuum evacuation vs traditional surgical evacuation

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ChiCTR1900023198 2019 *(Continued)*

Outcomes	The incidence of intrauterine adhesion
Starting date	12-Feb-2019
Contact information	
Notes	None

ChiCTR-TRC-08000725 2008

Study name	The and psychological outcomes of expectant management, surgical evacuation or medical evacuation with single dose 800 mcg vaginal misoprostol for women with first trimester miscarriage in a randomized controlled trial
Methods	A randomised, parallel group, three-arm, single-blinded study
Participants	180 women attending a university hospital in Hong Kong between 1st September 2008 to 5th September 2012 with a miscarriage of < 13 weeks gestation (both incomplete and missed miscarriage)
Interventions	Expectant management versus surgical evacuation versus misoprostol 800 micrograms
Outcomes	Complete miscarriage; women's views/satisfaction
Starting date	1st September 2008
Contact information	
Notes	Last updated 4th June 2015, no link to published record

Economides 2004

Study name	Non-surgical management of delayed miscarriage: a randomised trial
Methods	Randomised controlled trial
Participants	100 women attending a university hospital in the UK between unspecified dates with a miscarriage (exact gestation not specified)(missed miscarriage only)
Interventions	Misoprostol given orally or vaginally as an outpatient versus expectant management as an outpatient
Outcomes	Complete miscarriage; need for unplanned/emergency surgical procedure
Starting date	9th July 2003
Contact information	Not provided
Notes	Publication status listed as "Results overdue"

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Ethayarooban 2017

Study name	Safety and effectiveness of vacuum aspiration, compared to curettage for management of patients with first trimester miscarriage in a limited resource setting in Sri Lanka.
Methods	A randomised, parallel group, two-arm, single-blinded study
Participants	136 women attending a maternity Hospital in Sri Lanka between unspecified dates with a miscarriage of < 13 weeks of gestation (type of miscarriage not specified)
Interventions	Suction aspiration as an inpatient manual procedure versus dilatation and curettage as an inpatient procedure
Outcomes	Composite outcome of death or serious complication; need for unplanned/emergency surgical procedure; pain scores (visual analogue scale); cervical tear; mean duration of hospital stay (days)
Starting date	24th July 2017
Contact information	
Notes	Recruitment status listed as "Recruiting", last updated 3rd March 2019

EUCTR2007-007661-20-SE

Study name	Which is the optimal treatment for miscarriage with a gestational sac in the uterus and which factors can predict if the treatment will be successful?
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	240 women attending a university hospital in Sweden between unspecified dates with a miscarriage of <14 weeks gestation (incomplete miscarriage only)
Interventions	Misoprostol 800 micrograms given vaginally versus expectant management
Outcomes	Complete miscarriage; need for unplanned/ emergency surgical procedure; pelvic inflammatory disease, sepsis or endometritis; change in haemoglobin measurements before and after the miscarriage; re-admission to hospital; anxiety score; depression score
Starting date	21st April 2008
Contact information	Not stated in trial registry
Notes	Trial status listed as "Ongoing"

ISRCTN11046192 2020

Study name	Efficacy of mifepristone followed by misoprostol compared to misoprostol alone in first-trimester miscarriage treatment
Methods	Single centre 2-arm, blinded, placebo-controlled randomised controlled trial
Participants	Women diagnosed with first-trimester miscarriage (up to 9 weeks of gestation)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ISRCTN11046192 2020 *(Continued)*

Interventions	Mifepristone 200 mg or placebo given orally, both followed by misoprostol 800 micrograms given vaginally 36 to 48 hours after the oral pill.
Outcomes	Complete miscarriage; complications; adverse effects; acceptability of the treatment
Starting date	10-Apr-2019
Contact information	
Notes	Retrospectively registered

Kopalakrishnan 2014

Study name	Surgical, medical or expectant management of first trimester miscarriage and its implications on clinical and psychological outcomes - a randomized controlled trial
Methods	A randomised, parallel group, three-arm, unblinded study
Participants	180 women attending an unspecified healthcare facility with a miscarriage of < 14 weeks gestation
Interventions	Suction aspiration as an inpatient versus misoprostol 800 micrograms given vaginally + repeated 4-6 hours later if needed versus expectant management
Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/emergency surgical procedure; pelvic inflammatory disease, sepsis or endometritis; change in haemoglobin measurements before and after the miscarriage; days of bleeding; cervical tear; women's views/satisfaction; mean duration of hospital stay (days); nausea; vomiting; diarrhoea
Starting date	Anticipated start date 5th November 2014
Contact information	
Notes	Recruitment status listed as "pending", last updated 3rd March 2019

Otieno 2018

Study name	Outcomes of medical versus surgical management of first trimester incomplete abortion on among women admitted at Kampala International University Teaching Hospital (KIU -TH)
Methods	A randomised, parallel group, two-arm, unblinded study
Participants	100 women attending a university hospital in Uganda with a miscarriage of gestation ≤ 12 weeks of gestation (incomplete miscarriage only)
Interventions	Misoprostol versus suction aspiration as an inpatient manual procedure
Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/emergency surgical procedure; pain scores (visual analogue scale); pelvic inflammatory disease, sepsis or endometritis; women's views/satisfaction; mean duration of hospital stay (days); re-admission to hospital

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Otieno 2018 *(Continued)*

Starting date	1st November 2018
Contact information	
Notes	Recruitment status listed as "pending", last updated 17th August 2020

PACTR202009610896579 2020

Study name	Misoprostol versus manual vacuum aspiration for the treatment of first trimester incomplete miscarriage at university of Maiduguri teaching hospital. a randomized controlled study
Methods	Single-centre, 2-arm, unblinded, randomised controlled trial
Participants	Women with an incomplete miscarriage
Interventions	Misoprostol (dose and route not stated) versus manual vacuum aspiration
Outcomes	Complete miscarriage
Starting date	Not stated
Contact information	Not stated
Notes	None

PACTR202009857889210 2020

Study name	Sublingual misoprostol versus manual vacuum aspiration for treatment of incomplete abortion in Nigeria: a randomized control study
Methods	2-arm, unblinded, randomised controlled trial
Participants	Women with a first-trimester incomplete abortion, confirmed by a trans-abdominal ultrasound scan of the uterus
Interventions	Single-dose sublingual misoprostol 400 micrograms versus manual vacuum aspiration
Outcomes	Complete miscarriage; side effects and tolerability
Starting date	Not stated
Contact information	Not stated
Notes	None

Sutharshan 2017

Study name	Effectiveness of manual vacuum aspiration when compared to expectant care in achieving complete miscarriage in women with first trimester pregnancy loss- a randomized controlled trial

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Sutharshan 2017 *(Continued)*

Methods	A randomised, parallel group, two-arm, unblinded study
Participants	134 women attending a teaching hospital in Sri Lanka with a miscarriage ≤ 12 weeks of gestation
Interventions	Suction aspiration as an inpatient manual procedure versus expectant management as an outpatient
Outcomes	Complete miscarriage; composite outcome of death or serious complication; need for unplanned/emergency surgical procedure; pain scores (visual analogue scale); pelvic inflammatory disease, sepsis or endometritis; change in haemoglobin measurements before and after the miscarriage; cervical tear; women's views/satisfaction; mean duration of hospital stay (days)
Starting date	10th June 2017
Contact information	
Notes	Recruitment status listed as "recruiting", last updated 3rd March 2019

Unkels 2008

Study name	Is misoprostol a safe alternative to manual vacuum aspiration in women with incomplete abortions in developing countries?
Methods	Evaluator-blinded, single-centre, randomised controlled non-inferiority trial
Participants	180 women attending an unspecified healthcare facility in Tanzania with a miscarriage in the first trimester (exact gestation unspecified) (incomplete miscarriage only)
Interventions	Misoprostol 600 micrograms given orally every 4 hours for 3 doses versus suction aspiration as a manual procedure
Outcomes	Composite outcome of death or serious complication; pain scores (visual analogue scale); change in haemoglobin measurements before and after the miscarriage; women's views/satisfaction; nausea; vomiting; diarrhoea;
Starting date	11th February 2008
Contact information	PO box 228, Lindi, Tanzania
Notes	Overall trial status listed as "completed", recruitment status listed as "no longer recruiting", publication status listed as "results overdue", last updated 22nd Feb 2008

USG-MVA: ultrasound-guided manual vacuum aspiration.

DATA AND ANALYSES

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

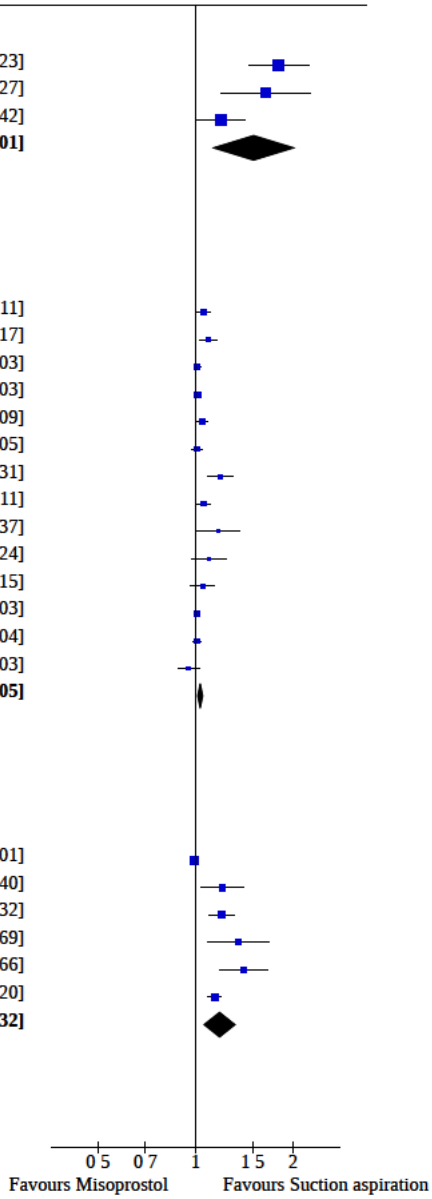
Comparison 1. Suction aspiration vs Misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Complete Miscarriage	23		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1.1 Missed miscarriage	3	308	Risk Ratio (IV, Random, 95% CI)	1.51 [1.14, 2.01]
1.1.2 Incomplete miscarriage	14	3474	Risk Ratio (IV, Random, 95% CI)	1.03 [1.01, 1.05]
1.1.3 Mixed population	6	1706	Risk Ratio (IV, Random, 95% CI)	1.19 [1.06, 1.32]
1.2 Composite outcome of death or serious complication	9	2146	Risk Ratio (IV, Random, 95% CI)	1.53 [0.45, 5.16]
1.3 Need for unplanned/emergency surgical procedure	9	1078	Risk Ratio (IV, Random, 95% CI)	0.19 [0.10, 0.37]
1.4 Pain score	8	2857	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.35, 0.51]
1.5 Pelvic inflammatory disease, sepsis or endometritis	12	2989	Risk Ratio (IV, Random, 95% CI)	1.27 [0.67, 2.41]
1.6 Change in haemoglobin measurements before and after the miscarriage	7	2706	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.29, -0.05]
1.7 Days of bleeding	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.8 Cervical tear	5	1252	Risk Ratio (IV, Random, 95% CI)	7.18 [0.84, 61.00]
1.9 Mean duration of hospital stay (days)	1	635	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.68, -0.12]
1.10 Re-admission to hospital	2	554	Risk Ratio (IV, Random, 95% CI)	0.77 [0.27, 2.21]
1.11 Nausea	13	3605	Risk Ratio (IV, Random, 95% CI)	0.52 [0.35, 0.76]
1.12 Vomiting	13	3447	Risk Ratio (IV, Random, 95% CI)	0.50 [0.38, 0.68]
1.13 Diarrhoea	9	1769	Risk Ratio (IV, Random, 95% CI)	0.39 [0.26, 0.60]
1.14 Pyrexia	15	4129	Risk Ratio (IV, Random, 95% CI)	0.37 [0.22, 0.61]
1.15 Anxiety score	2	719	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.24, 0.09]
1.16 Depression score	2	719	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.46, 0.12]

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.1. Comparison 1: Suction aspiration vs Misoprostol, Outcome 1: Complete Miscarriage

Study or Subgroup	Suction aspiration Events	Total	Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Missed miscarriage						
Graziosi 2004	72	75	42	79	34 7%	1 81 [1 46 , 2 23]
Muffley 2002	25	25	15	25	27 8%	1 65 [1 19 , 2 27]
Shaheen 2017	48	52	40	52	37 4%	1 20 [1 01 , 1 42]
Subtotal (95% CI)		**152**		**156**	**100.0%**	**1.51 [1.14 , 2.01]**
Total events:	145		97			
Heterogeneity: Tau² = 0 05; Chi² = 9 55, df = 2 (P = 0 008); I² = 79%						
Test for overall effect: Z = 2 83 (P = 0 005)						
1.1.2 Incomplete miscarriage						
Arellano 2009	97	97	100	106	6 8%	1 06 [1 01 , 1 11]
Bique 2007	101	101	101	111	5 4%	1 10 [1 03 , 1 17]
Chigbu 2012	160	160	158	160	12 4%	1 01 [0 99 , 1 03]
Dabash 2010	346	347	342	348	13 6%	1 01 [1 00 , 1 03]
Dao 2007	222	224	206	218	9 6%	1 05 [1 01 , 1 09]
Das 2014	109	111	108	111	8 5%	1 01 [0 97 , 1 05]
Ibiyemi 2018	97	98	83	100	3 0%	1 19 [1 09 , 1 31]
Montesinos 2011	97	97	100	106	6 8%	1 06 [1 01 , 1 11]
Nwafor 2020	44	46	39	48	1 3%	1 18 [1 01 , 1 37]
Patua 2013	48	50	42	48	1 9%	1 10 [0 97 , 1 24]
Sahin 2001	40	40	38	40	3 4%	1 05 [0 97 , 1 15]
Shwekerela 2007	150	150	149	150	13 0%	1 01 [0 99 , 1 03]
Taylor 2011	109	110	106	108	10 2%	1 01 [0 98 , 1 04]
Weeks 2005	75	82	103	107	4 0%	0 95 [0 88 , 1 03]
Subtotal (95% CI)		**1713**		**1761**	**100.0%**	**1.03 [1.01 , 1.05]**
Total events:	1695		1675			
Heterogeneity: Tau² = 0 00; Chi² = 36 15, df = 13 (P = 0 0006); I² = 64%						
Test for overall effect: Z = 3 59 (P = 0 0003)						
1.1.3 Mixed population						
Chung 1999	308	314	318	321	20 9%	0 99 [0 97 , 1 01]
Demetroulis 2001	40	40	33	40	15 2%	1 21 [1 04 , 1 40]
Ganguly 2010	59	60	98	120	18 4%	1 20 [1 10 , 1 32]
Kashif 2020	30	30	22	30	11 4%	1 36 [1 09 , 1 69]
Kong 2013	54	55	42	60	14 0%	1 40 [1 18 , 1 66]
Zhang 2005	143	148	412	488	20 2%	1 14 [1 09 , 1 20]
Subtotal (95% CI)		**647**		**1059**	**100.0%**	**1.19 [1.06 , 1.32]**
Total events:	634		925			
Heterogeneity: Tau² = 0 01; Chi² = 68 86, df = 5 (P < 0 00001); I² = 93%						
Test for overall effect: Z = 3 04 (P = 0 002)						
Test for subgroup differences: Chi² = 12 54, df = 2 (P = 0 002), I² = 84 0%						

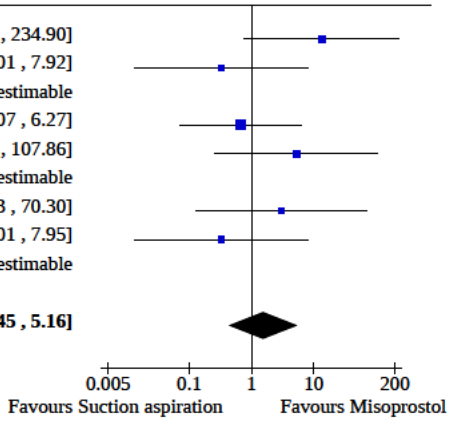


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.2. Comparison 1: Suction aspiration vs Misoprostol, Outcome 2: Composite outcome of death or serious complication

Study or Subgroup	Suction aspiration Events	Total	Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Chung 1999	6	314	0	321	16.8%	13.29 [0.75 , 234.90]
Dao 2007	0	224	1	218	13.7%	0.32 [0.01 , 7.92]
Demetroulis 2001	0	40	0	40		Not estimable
Ganguly 2010	1	60	3	120	26.5%	0.67 [0.07 , 6.27]
Graziosi 2004	2	75	0	79	15.3%	5.26 [0.26 , 107.86]
Ibiyemi 2018	0	98	0	100		Not estimable
Muffley 2002	1	25	0	25	14.1%	3.00 [0.13 , 70.30]
Taylor 2011	0	110	1	108	13.8%	0.33 [0.01 , 7.95]
Weeks 2005	0	82	0	107		Not estimable
Total (95% CI)		**1028**		**1118**	**100.0%**	**1.53 [0.45 , 5.16]**
Total events:	10		5			

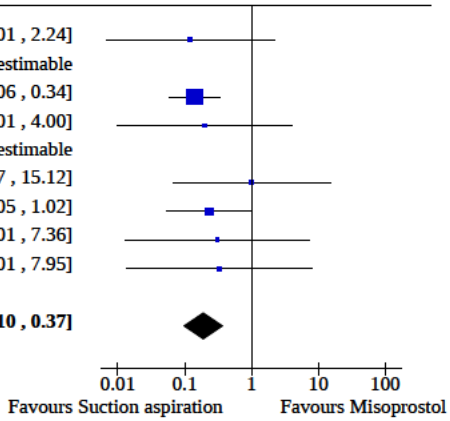
Heterogeneity: Tau² = 0.14; Chi² = 5 32, df = 5 (P = 0.38); I² = 6%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Suction aspiration vs Misoprostol, Outcome 3: Need for unplanned/emergency surgical procedure

Study or Subgroup	Suction aspiration Events	Total	Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bique 2007	0	101	4	111	5.1%	0.12 [0.01 , 2.24]
Demetroulis 2001	0	40	0	40		Not estimable
Graziosi 2004	5	75	37	79	55.9%	0.14 [0.06 , 0.34]
Kashif 2020	0	30	2	30	4.8%	0.20 [0.01 , 4.00]
Kong 2013	0	55	0	59		Not estimable
Muffley 2002	1	25	1	25	5.9%	1.00 [0.07 , 15.12]
Nwafor 2020	2	46	9	48	19.8%	0.23 [0.05 , 1.02]
Patua 2013	0	50	1	46	4.3%	0.31 [0.01 , 7.36]
Taylor 2011	0	110	1	108	4.2%	0.33 [0.01 , 7.95]
Total (95% CI)		**532**		**546**	**100.0%**	**0.19 [0.10 , 0.37]**
Total events:	8		55			

Heterogeneity: Tau² = 0.00; Chi² = 2 21, df = 6 (P = 0.90); I² = 0%
Test for overall effect: Z = 4.96 (P < 0.00001)
Test for subgroup differences: Not applicable

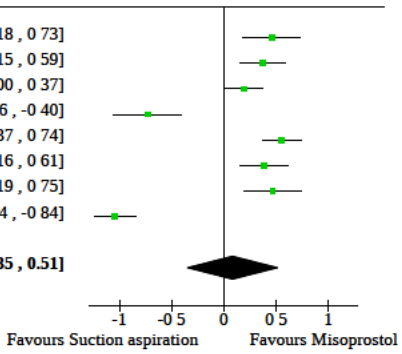


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.4. Comparison 1: Suction aspiration vs Misoprostol, Outcome 4: Pain score

Study or Subgroup	Suction aspiration Mean	SD	Total	Misoprostol Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bique 2007	4 21	3 44	101	2 63	3 44	111	12 4%	0 46 [0 18 , 0 73]
Chigbu 2012	4 5	4 04	160	3	4 04	160	12 6%	0 37 [0 15 , 0 59]
Dao 2007	2 73	2 18	224	2 32	2 18	218	12 7%	0 19 [0 00 , 0 37]
Graziosi 2004	3	2 4	75	5	3	79	12 1%	-0 73 [-1 06 , -0 40]
Harwood 2008	45 84	10 95	150	40 04	10 31	457	12 7%	0 55 [0 37 , 0 74]
Shwekerela 2007	3 5	1 3	150	3	1 3	150	12 6%	0 38 [0 16 , 0 61]
Taylor 2011	4 6	2 99	112	3 2	2 99	93	12 3%	0 47 [0 19 , 0 75]
Zhang 2005	3 2	2 4	141	5 7	2 4	476	12 7%	-1 04 [-1 24 , -0 84]
Total (95% CI)			**1113**			**1744**	**100.0%**	**0.08 [-0.35 , 0.51]**

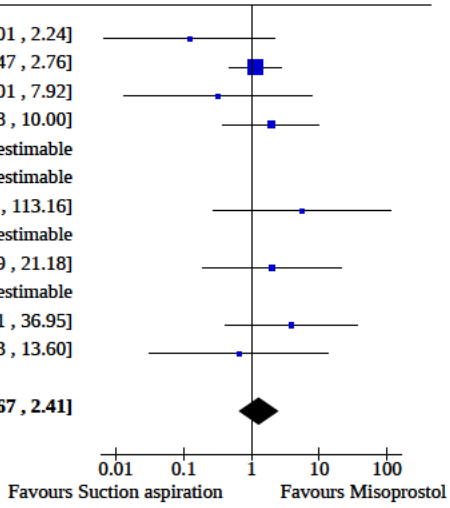
Heterogeneity: Tau² = 0 37; Chi² = 202 17, df = 7 (P < 0 00001); I² = 97%
Test for overall effect: Z = 0 38 (P = 0 71)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Suction aspiration vs Misoprostol, Outcome 5: Pelvic inflammatory disease, sepsis or endometritis

Study or Subgroup	Suction aspiration Events	Total	Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bique 2007	0	101	4	111	4.8%	0.12 [0.01 , 2.24]
Chung 1999	10	314	9	321	51.7%	1.14 [0.47 , 2.76]
Dao 2007	0	224	1	218	4.0%	0.32 [0.01 , 7.92]
Demetroulis 2001	4	38	2	37	15.2%	1 95 [0.38 , 10.00]
Graziosi 2004	0	75	0	79		Not estimable
Kashif 2020	0	30	0	30		Not estimable
Kong 2013	2	53	0	59	4.5%	5.56 [0.27 , 113.16]
Nwafor 2020	0	46	0	48		Not estimable
Sahin 2001	2	40	1	40	7.3%	2.00 [0.19 , 21.18]
Shwekerela 2007	0	150	0	150		Not estimable
Weeks 2005	3	82	1	107	8.1%	3 91 [0.41 , 36.95]
Zhang 2005	0	148	2	488	4.4%	0.66 [0.03 , 13.60]
Total (95% CI)		**1301**		**1688**	**100.0%**	**1.27 [0.67 , 2.41]**
Total events:	21		20			

Heterogeneity: Tau² = 0.00; Chi² = 5.73, df = 7 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable

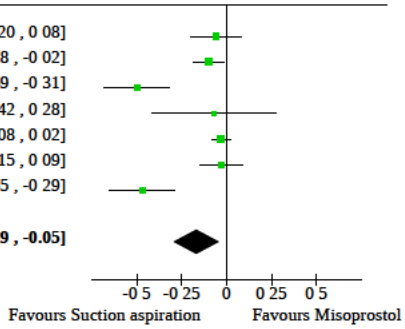


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.6. Comparison 1: Suction aspiration vs Misoprostol, Outcome 6: Change in haemoglobin measurements before and after the miscarriage

Study or Subgroup	Suction aspiration Mean	SD	Total	Misoprostol Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chung 1999	0 28	0 7	314	0 34	1 1	321	14 9%	-0 06 [-0 20 , 0 08]
Dabash 2010	0 4	0 55	337	0 5	0 55	335	17 3%	-0 10 [-0 18 , -0 02]
Davis 2007	0 2	0 9	134	0 7	1 1	422	13 1%	-0 50 [-0 69 , -0 31]
Kong 2013	0 12	0 84	53	0 19	1 03	59	7 4%	-0 07 [-0 42 , 0 28]
Patua 2013	0 19	0 12	50	0 22	0 13	46	18 3%	-0 03 [-0 08 , 0 02]
Sahin 2001	0 38	0 26	40	0 41	0 29	40	15 9%	-0 03 [-0 15 , 0 09]
Zhang 2005	0 18	0 89	134	0 65	1 1	421	13 1%	-0 47 [-0 65 , -0 29]
Total (95% CI)			**1062**			**1644**	**100.0%**	**-0.17 [-0.29 , -0.05]**

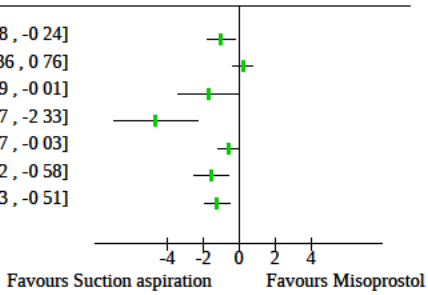
Heterogeneity: Tau² = 0 02; Chi² = 41 85, df = 6 (P < 0 00001); I² = 86%
Test for overall effect: Z = 2 75 (P = 0 006)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Suction aspiration vs Misoprostol, Outcome 7: Days of bleeding

Study or Subgroup	Suction aspiration Mean	SD	Total	Misoprostol Mean	SD	Total	Mean Difference IV, Random, 95% CI
Braham 2016	2 67	1 2	30	3 68	1 8	30	-1 01 [-1 78 , -0 24]
Chung 1999	9 3	3 57	314	9 1	3 57	321	0 20 [-0 36 , 0 76]
Graziosi 2004	8 7	5 1	75	10 4	5 6	79	-1 70 [-3 39 , -0 01]
Kong 2013	10 73	5 92	53	15 38	6 63	59	-4 65 [-6 97 , -2 33]
Montesinos 2011	3 1	2 06	97	3 7	2 06	106	-0 60 [-1 17 , -0 03]
Sahin 2001	4 9	2 19	40	6 45	2 23	40	-1 55 [-2 52 , -0 58]
Taylor 2011	1 64	2 6	112	2 86	2 6	93	-1 22 [-1 93 , -0 51]

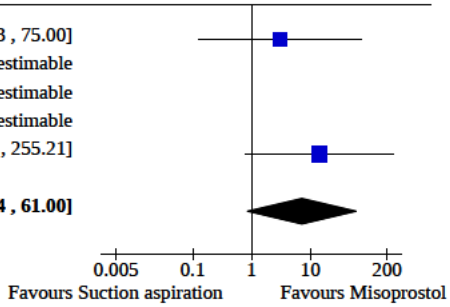
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Suction aspiration vs Misoprostol, Outcome 8: Cervical tear

Study or Subgroup	Suction aspiration Events	Total	Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Chung 1999	1	314	0	321	44.8%	3.07 [0.13 , 75.00]
Ganguly 2010	0	60	0	120		Not estimable
Graziosi 2004	0	75	0	79		Not estimable
Nwafor 2020	0	46	0	48		Not estimable
Weeks 2005	5	82	0	107	55.2%	14.31 [0.80 , 255.21]
Total (95% CI)		**577**		**675**	**100.0%**	**7.18 [0.84 , 61.00]**
Total events:	6		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.80 (P = 0.07)
Test for subgroup differences: Not applicable

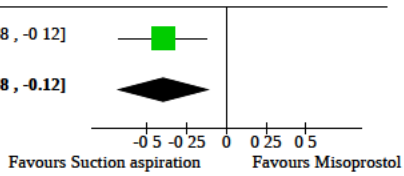


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.9. Comparison 1: Suction aspiration vs Misoprostol, Outcome 9: Mean duration of hospital stay (days)

Study or Subgroup	Suction aspiration Mean	SD	Total	Misoprostol Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chung 1999	1 78	1 79	314	2 18	1 79	321	100 0%	-0 40 [-0 68 , -0 12]
Total (95% CI)			**314**			**321**	**100.0%**	**-0.40 [-0.68 , -0.12]**

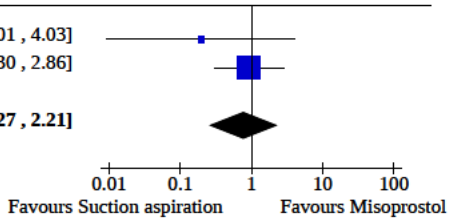
Heterogeneity: Not applicable
Test for overall effect: Z = 2 82 (P = 0 005)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Suction aspiration vs Misoprostol, Outcome 10: Re-admission to hospital

Study or Subgroup	Suction aspiration Events	Total	Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Dao 2007	0	224	2	218	12.2%	0.19 [0.01 , 4.03]
Kong 2013	5	53	6	59	87.8%	0.93 [0.30 , 2.86]
Total (95% CI)		**277**		**277**	**100.0%**	**0.77 [0.27 , 2.21]**
Total events:	5		8			

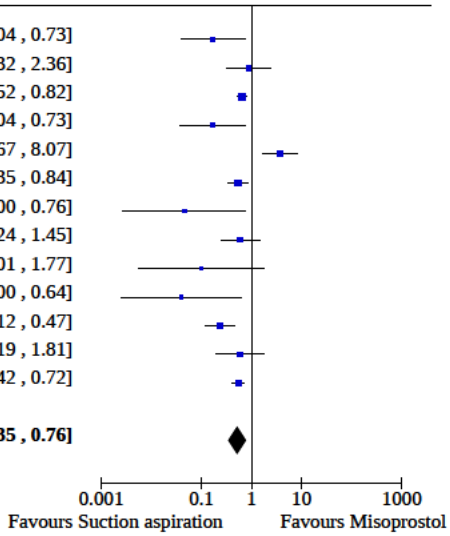
Heterogeneity: Tau² = 0.00; Chi² = 0 90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Suction aspiration vs Misoprostol, Outcome 11: Nausea

Study or Subgroup	Suction aspiration Events	Total	Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bique 2007	2	101	13	111	4.8%	0.17 [0.04 , 0.73]
Chigbu 2012	7	160	8	160	7.7%	0.88 [0.32 , 2.36]
Dabash 2010	83	316	132	327	15.0%	0.65 [0.52 , 0.82]
Dao 2007	2	224	12	223	4.7%	0.17 [0.04 , 0.73]
Demetroulis 2001	22	40	6	40	9.5%	3.67 [1.67 , 8.07]
Ganguly 2010	17	60	63	120	13.1%	0.54 [0.35 , 0.84]
Graziosi 2004	0	75	11	79	1.7%	0.05 [0.00 , 0.76]
Ibiyemi 2018	7	98	12	100	8.5%	0.60 [0.24 , 1.45]
Montesinos 2011	0	97	5	106	1.6%	0.10 [0.01 , 1.77]
Muffley 2002	0	25	12	25	1.7%	0.04 [0.00 , 0.64]
Shwekerela 2007	9	150	38	150	10.4%	0.24 [0.12 , 0.47]
Taylor 2011	5	112	7	93	6.8%	0.59 [0.19 , 1.81]
Zhang 2005	41	141	250	472	14.7%	0.55 [0.42 , 0.72]
Total (95% CI)		**1599**		**2006**	**100.0%**	**0.52 [0.35 , 0.76]**
Total events:	195		569			

Heterogeneity: Tau² = 0.24; Chi² = 42.91, df = 12 (P < 0.0001); I² = 72%
Test for overall effect: Z = 3.39 (P = 0.0007)
Test for subgroup differences: Not applicable

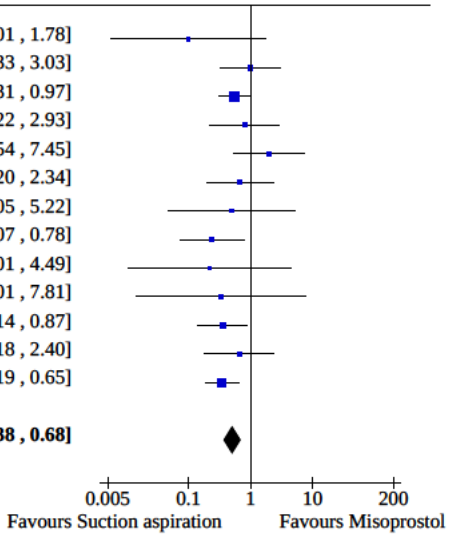


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.12. Comparison 1: Suction aspiration vs Misoprostol, Outcome 12: Vomiting

Study or Subgroup	Suction aspiration Events	Total	Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bique 2007	0	101	5	111	1.1%	0.10 [0.01 , 1.78]
Chigbu 2012	6	160	6	160	7.1%	1.00 [0.33 , 3.03]
Dabash 2010	17	316	32	327	27.3%	0.55 [0.31 , 0.97]
Dao 2007	4	224	5	223	5.2%	0.80 [0.22 , 2.93]
Demetroulis 2001	6	40	3	40	5.1%	2.00 [0.54 , 7.45]
Ibiyemi 2018	4	98	6	100	5.8%	0.68 [0.20 , 2.34]
Kashif 2020	1	30	2	30	1.6%	0.50 [0.05 , 5.22]
Kong 2013	3	53	14	59	6.2%	0.24 [0.07 , 0.78]
Montesinos 2011	0	97	2	106	1.0%	0.22 [0.01 , 4.49]
Muffley 2002	0	25	1	25	0.9%	0.33 [0.01 , 7.81]
Shwekerela 2007	6	150	17	150	10.8%	0.35 [0.14 , 0.87]
Taylor 2011	4	112	5	93	5.3%	0.66 [0.18 , 2.40]
Zhang 2005	10	142	96	475	22.6%	0.35 [0.19 , 0.65]
Total (95% CI)		**1548**		**1899**	**100.0%**	**0.50 [0.38 , 0.68]**
Total events:	61		194			

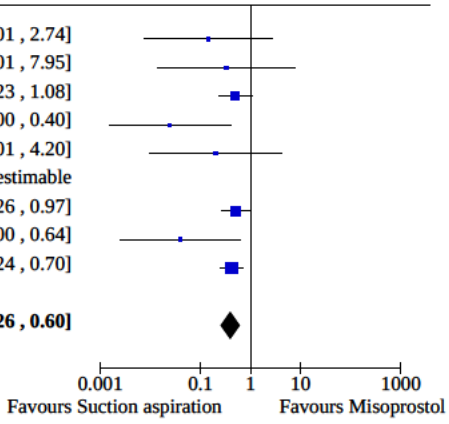
Heterogeneity: Tau² = 0.00; Chi² = 11.69, df = 12 (P = 0.47); I² = 0%
Test for overall effect: Z = 4.52 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Suction aspiration vs Misoprostol, Outcome 13: Diarrhoea

Study or Subgroup	Suction aspiration Events	Total	Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Chigbu 2012	0	160	3	160	1.9%	0.14 [0.01 , 2.74]
Demetroulis 2001	0	40	1	40	1.7%	0.33 [0.01 , 7.95]
Ganguly 2010	7	60	28	120	22.6%	0.50 [0.23 , 1.08]
Graziosi 2004	0	75	21	79	2.2%	0.02 [0.00 , 0.40]
Ibiyemi 2018	0	98	2	100	1.9%	0.20 [0.01 , 4.20]
Kashif 2020	0	30	0	30		Not estimable
Kong 2013	10	53	22	59	29.0%	0.51 [0.26 , 0.97]
Muffley 2002	0	25	12	25	2.2%	0.04 [0.00 , 0.64]
Zhang 2005	14	142	113	473	38.5%	0.41 [0.24 , 0.70]
Total (95% CI)		**683**		**1086**	**100.0%**	**0.39 [0.26 , 0.60]**
Total events:	31		202			

Heterogeneity: Tau² = 0.05; Chi² = 8.00, df = 7 (P = 0.33); I² = 13%
Test for overall effect: Z = 4.39 (P < 0.0001)
Test for subgroup differences: Not applicable

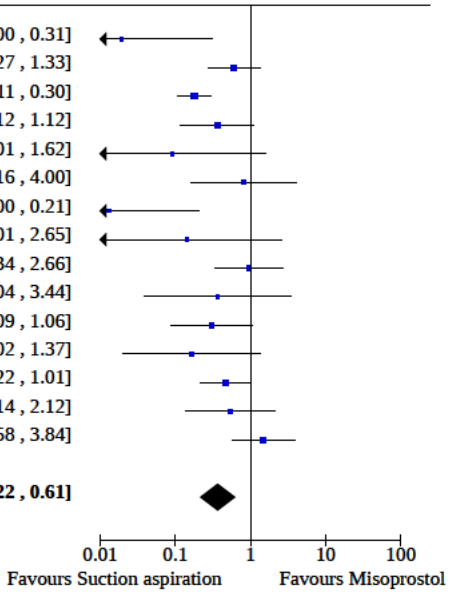


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.14. Comparison 1: Suction aspiration vs Misoprostol, Outcome 14: Pyrexia

Study or Subgroup	Suction aspiration Events	Total	Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bique 2007	0	101	28	111	2.8%	0.02 [0.00 , 0.31]
Chigbu 2012	9	160	15	160	10.5%	0.60 [0.27 , 1.33]
Dabash 2010	16	316	93	327	12.3%	0.18 [0.11 , 0.30]
Dao 2007	4	224	11	223	8.4%	0.36 [0.12 , 1.12]
Das 2014	0	111	5	111	2.6%	0.09 [0.01 , 1.62]
Ganguly 2010	2	60	5	120	5.9%	0.80 [0.16 , 4.00]
Ibiyemi 2018	0	98	39	100	2.8%	0.01 [0.00 , 0.21]
Kashif 2020	0	30	3	30	2.6%	0.14 [0.01 , 2.65]
Kong 2013	6	53	7	59	9.0%	0.95 [0.34 , 2.66]
Montesinos 2011	1	97	3	106	3.9%	0.36 [0.04 , 3.44]
Patua 2013	3	50	9	46	7.7%	0.31 [0.09 , 1.06]
Shwekerela 2007	1	150	6	150	4.2%	0.17 [0.02 , 1.37]
Taylor 2011	9	112	16	93	10.7%	0.47 [0.22 , 1.01]
Weeks 2005	3	147	6	159	7.1%	0.54 [0.14 , 2.12]
Zhang 2005	6	148	13	477	9.5%	1.49 [0.58 , 3.84]
Total (95% CI)		**1857**		**2272**	**100.0%**	**0.37 [0.22 , 0.61]**
Total events:	60		259			

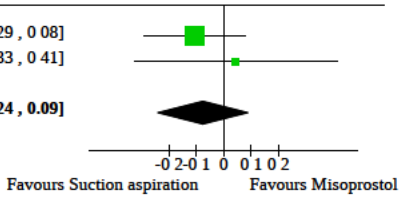
Heterogeneity: Tau² = 0.50; Chi² = 34.35, df = 14 (P = 0.002); I² = 59%
Test for overall effect: Z = 3.80 (P = 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Suction aspiration vs Misoprostol, Outcome 15: Anxiety score

Study or Subgroup	Suction aspiration Mean	SD	Total	Misoprostol Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Harwood 2008	2 33	1 04	150	2 45	1 15	457	80 2%	-0 11 [-0 29 , 0 08]
Kong 2013	58 62	10 56	53	58 08	13 57	59	19 8%	0 04 [-0 33 , 0 41]
Total (95% CI)			**203**			**516**	**100.0%**	**-0.08 [-0.24 , 0.09]**

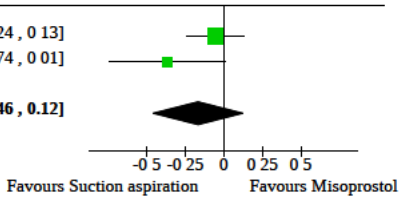
Heterogeneity: Tau² = 0 00; Chi² = 0 51, df = 1 (P = 0 48); I² = 0%
Test for overall effect: Z = 0 91 (P = 0 36)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Suction aspiration vs Misoprostol, Outcome 16: Depression score

Study or Subgroup	Suction aspiration Mean	SD	Total	Misoprostol Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Harwood 2008	2 8	0 88	150	2 85	0 89	457	64 2%	-0 06 [-0 24 , 0 13]
Kong 2013	5 3	6 91	53	8 75	11 05	59	35 8%	-0 37 [-0 74 , 0 01]
Total (95% CI)			**203**			**516**	**100.0%**	**-0.17 [-0.46 , 0.12]**

Heterogeneity: Tau² = 0 03; Chi² = 2 14, df = 1 (P = 0 14); I² = 53%
Test for overall effect: Z = 1 12 (P = 0 26)
Test for subgroup differences: Not applicable

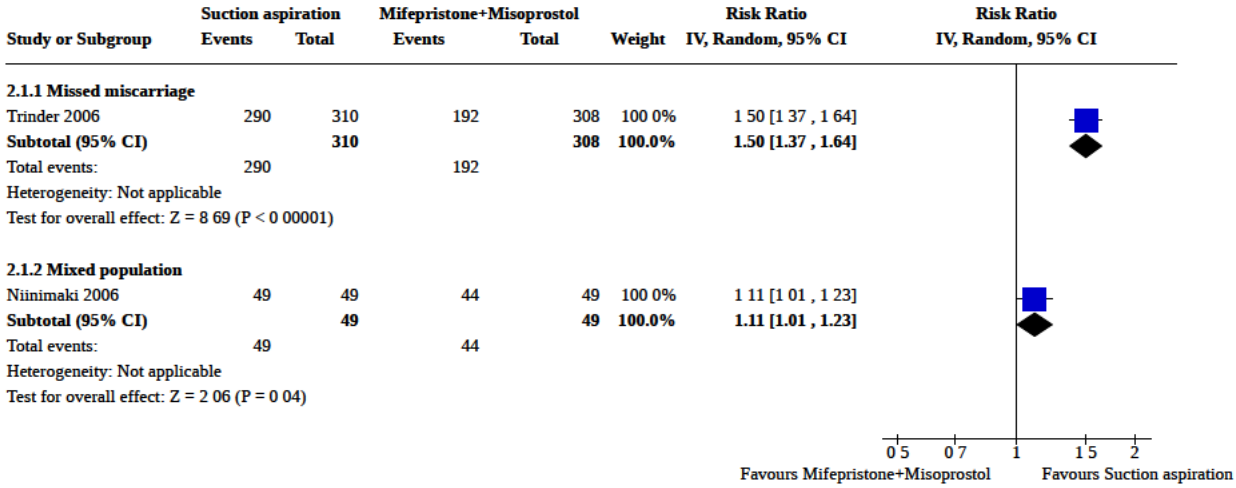


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Comparison 2. Suction aspiration vs Mifepristone + Misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Complete Miscarriage	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1.1 Missed miscarriage	1	618	Risk Ratio (IV, Random, 95% CI)	1.50 [1.37, 1.64]
2.1.2 Mixed population	1	98	Risk Ratio (IV, Random, 95% CI)	1.11 [1.01, 1.23]
2.2 Composite outcome of death or serious complication	1	618	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.74]
2.3 Need for unplanned/emergency surgical procedure	1	98	Risk Ratio (IV, Random, 95% CI)	1.00 [0.06, 15.54]
2.4 Pelvic inflammatory disease, sepsis or endometritis	2	716	Risk Ratio (IV, Random, 95% CI)	2.33 [0.47, 11.44]
2.5 Re-admission to hospital	1	98	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.69]

Analysis 2.1. Comparison 2: Suction aspiration vs Mifepristone + Misoprostol, Outcome 1: Complete Miscarriage

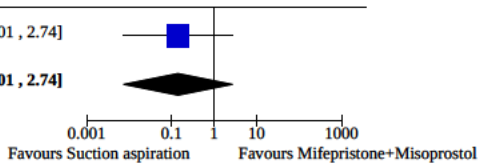


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 2.2. Comparison 2: Suction aspiration vs Mifepristone + Misoprostol, Outcome 2: Composite outcome of death or serious complication

Study or Subgroup	Suction aspiration Events	Total	Mifepristone+Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Trinder 2006	0	310	3	308	100.0%	0.14 [0.01 , 2.74]
Total (95% CI)		**310**		**308**	**100.0%**	**0.14 [0.01 , 2.74]**
Total events:	0		3			

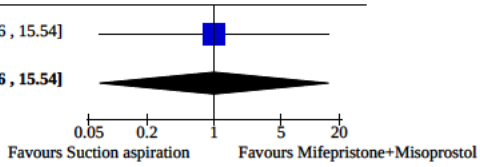
Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Suction aspiration vs Mifepristone + Misoprostol, Outcome 3: Need for unplanned/emergency surgical procedure

Study or Subgroup	Suction aspiration Events	Total	Mifepristone+Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Niinimaki 2006	1	49	1	49	100.0%	1.00 [0.06 , 15.54]
Total (95% CI)		**49**		**49**	**100.0%**	**1.00 [0.06 , 15.54]**
Total events:	1		1			

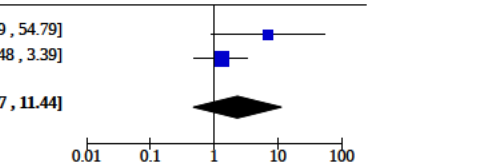
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Suction aspiration vs Mifepristone + Misoprostol, Outcome 4: Pelvic inflammatory disease, sepsis or endometritis

Study or Subgroup	Suction aspiration Events	Total	Mifepristone+Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Niinimaki 2006	7	49	1	49	35.2%	7.00 [0.89 , 54.79]
Trinder 2006	9	310	7	308	64.8%	1.28 [0.48 , 3.39]
Total (95% CI)		**359**		**357**	**100.0%**	**2.33 [0.47 , 11.44]**
Total events:	16		8			

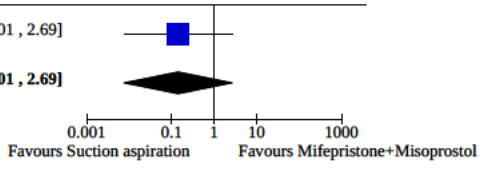
Heterogeneity: $Tau^2 = 0.77$; $Chi^2 = 2.14$, df = 1 (P = 0.14); $I^2 = 53\%$
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Suction aspiration vs Mifepristone + Misoprostol, Outcome 5: Re-admission to hospital

Study or Subgroup	Suction aspiration Events	Total	Mifepristone+Misoprostol Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Niinimaki 2006	0	49	3	49	100.0%	0.14 [0.01 , 2.69]
Total (95% CI)		**49**		**49**	**100.0%**	**0.14 [0.01 , 2.69]**
Total events:	0		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

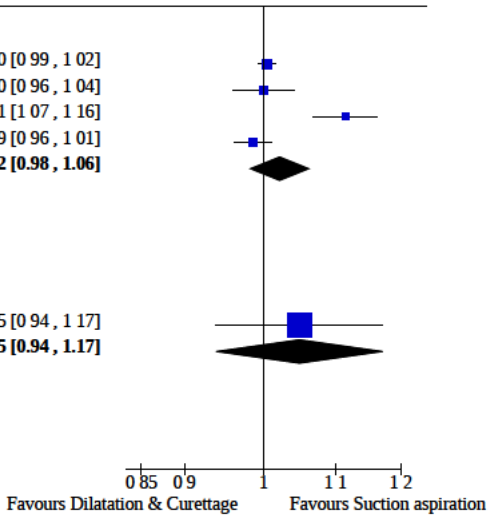
Comparison 3. Suction aspiration vs Dilatation & Curettage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Complete Miscarriage	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1.1 Incomplete miscarriage	4	1432	Risk Ratio (IV, Random, 95% CI)	1.02 [0.98, 1.06]
3.1.2 Mixed population	1	90	Risk Ratio (IV, Random, 95% CI)	1.05 [0.94, 1.17]
3.2 Composite outcome of death or serious complication	5	1521	Risk Ratio (IV, Random, 95% CI)	1.27 [0.80, 2.02]
3.3 Need for unplanned/emergency surgical procedure	2	693	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 8.07]
3.4 Pelvic inflammatory disease, sepsis or endometritis	3	822	Risk Ratio (IV, Random, 95% CI)	0.77 [0.53, 1.11]
3.5 Mean volumes of blood loss (millilitres)	2	451	Mean Difference (IV, Random, 95% CI)	-11.44 [-21.49, -1.40]
3.6 Change in haemoglobin measurements before and after the miscarriage	2	370	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.68, -0.14]
3.7 Days of bleeding	1	270	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.30, 0.70]
3.8 Cervical tear	2	558	Risk Ratio (IV, Random, 95% CI)	0.49 [0.20, 1.18]
3.9 Mean duration of hospital stay (days)	3	220	Mean Difference (IV, Random, 95% CI)	-0.56 [-0.89, -0.23]
3.10 Re-admission to hospital	2	1042	Risk Ratio (IV, Random, 95% CI)	1.61 [0.62, 4.16]
3.11 Vomiting	1	599	Risk Ratio (IV, Random, 95% CI)	2.31 [0.60, 8.85]
3.12 Pyrexia	3	1157	Risk Ratio (IV, Random, 95% CI)	1.31 [0.85, 2.02]

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

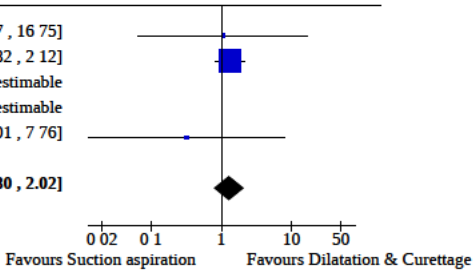
Analysis 3.1. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 1: Complete Miscarriage

Study or Subgroup	Suction aspiration Events	Total	Dilatation & Curettage Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Incomplete miscarriage						
Caceres 1979	223	223	234	235	29 0%	1 00 [0 99 , 1 02]
Kittiwatanakul 2012	47	47	47	47	22 4%	1 00 [0 96 , 1 04]
Salam 2016	301	305	270	305	22 0%	1 11 [1 07 , 1 16]
Verkuyl 1993	136	138	132	132	26 6%	0 99 [0 96 , 1 01]
Subtotal (95% CI)		**713**		**719**	**100.0%**	**1.02 [0.98 , 1.06]**
Total events:	707		683			
Heterogeneity: Tau² = 0 00; Chi² = 25 25, df = 3 (P < 0 0001); I² = 88%						
Test for overall effect: Z = 1 08 (P = 0 28)						
3.1.2 Mixed population						
Arif 2018	43	45	41	45	100 0%	1 05 [0 94 , 1 17]
Subtotal (95% CI)		**45**		**45**	**100.0%**	**1.05 [0.94 , 1.17]**
Total events:	43		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0 84 (P = 0 40)						
Test for subgroup differences: Chi² = 0 19, df = 1 (P = 0 66), I² = 0%						



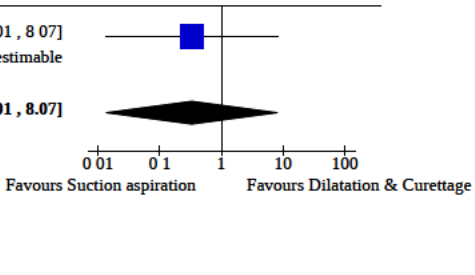
Analysis 3.2. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 2: Composite outcome of death or serious complication

Study or Subgroup	Suction aspiration Events	Total	Dilatation & Curettage Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Caceres 1979	1	223	1	235	2 8%	1 05 [0 07 , 16 75]
Caceres 1981	36	301	27	298	95 1%	1 32 [0 82 , 2 12]
Kittiwatanakul 2012	0	47	0	47		Not estimable
Pereira 2006	0	50	0	50		Not estimable
Verkuyl 1993	0	138	1	132	2 1%	0 32 [0 01 , 7 76]
Total (95% CI)		**759**		**762**	**100.0%**	**1.27 [0.80 , 2.02]**
Total events:	37		29			
Heterogeneity: Tau² = 0 00; Chi² = 0 76, df = 2 (P = 0 68); I² = 0%						
Test for overall effect: Z = 1 03 (P = 0 30)						
Test for subgroup differences: Not applicable						



Analysis 3.3. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 3: Need for unplanned/emergency surgical procedure

Study or Subgroup	Suction aspiration Events	Total	Dilatation & Curettage Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Caceres 1981	0	301	1	298	100 0%	0 33 [0 01 , 8 07]
Kittiwatanakul 2012	0	47	0	47		Not estimable
Total (95% CI)		**348**		**345**	**100.0%**	**0.33 [0.01 , 8.07]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0 68 (P = 0 50)						
Test for subgroup differences: Not applicable						

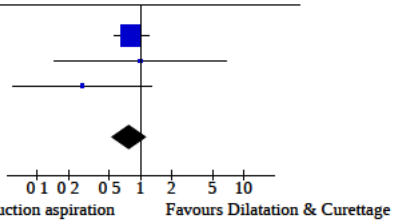


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 3.4. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 4: Pelvic inflammatory disease, sepsis or endometritis

Study or Subgroup	Suction aspiration Events	Total	Dilatation & Curettage Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Caceres 1979	37	223	48	235	90 6%	0 81 [0 55 , 1 20]
Kittiwatanakul 2012	2	47	2	47	3 7%	1 00 [0 15 , 6 81]
Verkuyl 1993	2	138	7	132	5 6%	0 27 [0 06 , 1 29]
Total (95% CI)		**408**		**414**	**100.0%**	**0.77 [0.53 , 1.11]**
Total events:	41		57			

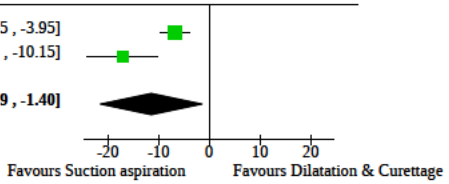
Heterogeneity: Tau² = 0 00; Chi² = 1 85, df = 2 (P = 0 40); I² = 0%
Test for overall effect: Z = 1 39 (P = 0 16)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 5: Mean volumes of blood loss (millilitres)

Study or Subgroup	Suction aspiration Mean	SD	Total	Dilatation & Curettage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kittiwatanakul 2012	30.4	7.3	47	37.2	6.8	47	54.9%	-6.80 [-9.65 , -3.95]
Verkuyl 1993	19.2	25.6	179	36.3	39.8	178	45.1%	-17.10 [-24.05 , -10.15]
Total (95% CI)			**226**			**225**	**100.0%**	**-11.44 [-21.49 , -1.40]**

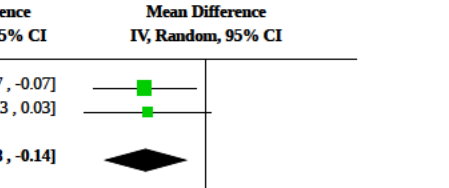
Heterogeneity: Tau² = 45.71; Chi² = 7.23, df = 1 (P = 0.007); I² = 86%
Test for overall effect: Z = 2.23 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 6: Change in haemoglobin measurements before and after the miscarriage

Study or Subgroup	Suction aspiration Mean	SD	Total	Dilatation & Curettage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Pereira 2006	0.63	0.89	50	1.05	0.89	50	60.4%	-0.42 [-0.77 , -0.07]
Verkuyl 1993	0.3	1.7	138	0.7	1.9	132	39.6%	-0.40 [-0.83 , 0.03]
Total (95% CI)			**188**			**182**	**100.0%**	**-0.41 [-0.68 , -0.14]**

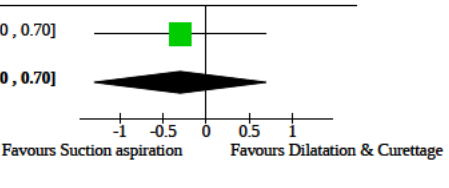
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 2.98 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 7: Days of bleeding

Study or Subgroup	Suction aspiration Mean	SD	Total	Dilatation & Curettage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Verkuyl 1993	4.9	3.8	138	5.2	4.5	132	100.0%	-0.30 [-1.30 , 0.70]
Total (95% CI)			**138**			**132**	**100.0%**	**-0.30 [-1.30 , 0.70]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.55)
Test for subgroup differences: Not applicable

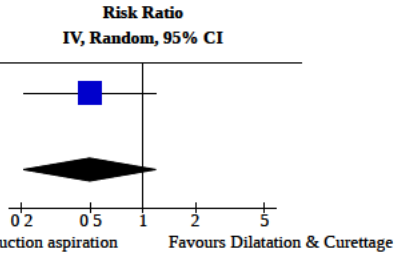


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 3.8. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 8: Cervical tear

Study or Subgroup	Suction aspiration Events	Total	Dilatation & Curettage Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Caceres 1979	7	223	15	235	100 0%	0 49 [0 20 , 1 18]
Pereira 2006	0	50	0	50		Not estimable
Total (95% CI)		**273**		**285**	**100.0%**	**0.49 [0.20 , 1.18]**
Total events:	7		15			

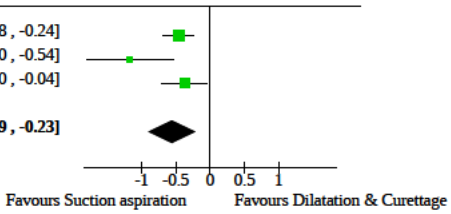
Heterogeneity: Not applicable
Test for overall effect: Z = 1 58 (P = 0 11)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 9: Mean duration of hospital stay (days)

Study or Subgroup	Suction aspiration Mean	SD	Total	Dilatation & Curettage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Arif 2018	0.24	0.54	45	0.7	0.54	45	45.3%	-0.46 [-0.68 , -0.24]
Fonseca 1997	0.35	0.88	15	1.52	0.88	15	18.4%	-1.17 [-1.80 , -0.54]
Pereira 2006	0.59	0.84	50	0.96	0.84	50	36.3%	-0.37 [-0.70 , -0.04]
Total (95% CI)			**110**			**110**	**100.0%**	**-0.56 [-0.89 , -0.23]**

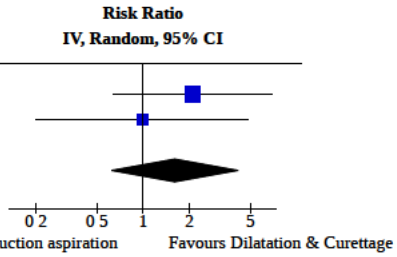
Heterogeneity: Tau² = 0.05; Chi² = 5.06, df = 2 (P = 0.08); I² = 60%
Test for overall effect: Z = 3.33 (P = 0.0009)
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 10: Re-admission to hospital

Study or Subgroup	Suction aspiration Events	Total	Dilatation & Curettage Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Caceres 1979	8	216	4	227	64 3%	2 10 [0 64 , 6 88]
Caceres 1981	3	301	3	298	35 7%	0 99 [0 20 , 4 87]
Total (95% CI)		**517**		**525**	**100.0%**	**1.61 [0.62 , 4.16]**
Total events:	11		7			

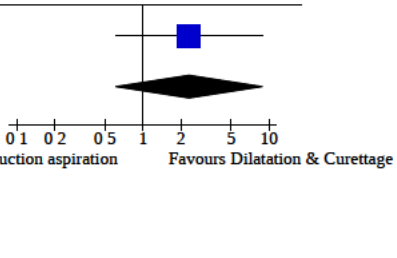
Heterogeneity: Tau² = 0 00; Chi² = 0 55, df = 1 (P = 0 46); I² = 0%
Test for overall effect: Z = 0 98 (P = 0 33)
Test for subgroup differences: Not applicable



Analysis 3.11. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 11: Vomiting

Study or Subgroup	Suction aspiration Events	Total	Dilatation & Curettage Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Caceres 1981	7	301	3	298	100 0%	2 31 [0 60 , 8 85]
Total (95% CI)		**301**		**298**	**100.0%**	**2.31 [0.60 , 8.85]**
Total events:	7		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1 22 (P = 0 22)
Test for subgroup differences: Not applicable

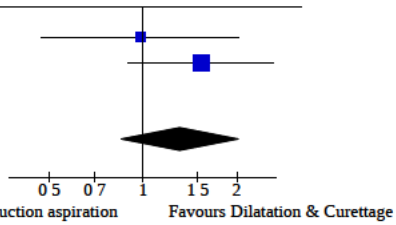


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 3.12. Comparison 3: Suction aspiration vs Dilatation & Curettage, Outcome 12: Pyrexia

Study or Subgroup	Suction aspiration Events	Total	Dilatation & Curettage Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Caceres 1979	13	223	14	235	35 1%	0 98 [0 47 , 2 04]
Caceres 1981	31	301	20	298	64 9%	1 53 [0 90 , 2 63]
Pereira 2006	0	50	0	50		Not estimable
Total (95% CI)		**574**		**583**	**100.0%**	**1.31 [0.85 , 2.02]**
Total events:	44		34			

Heterogeneity: Tau² = 0 00; Chi² = 0 94, df = 1 (P = 0 33); I² = 0%
Test for overall effect: Z = 1 22 (P = 0 22)
Test for subgroup differences: Not applicable



Comparison 4. Suction aspiration vs Expectant/ Placebo

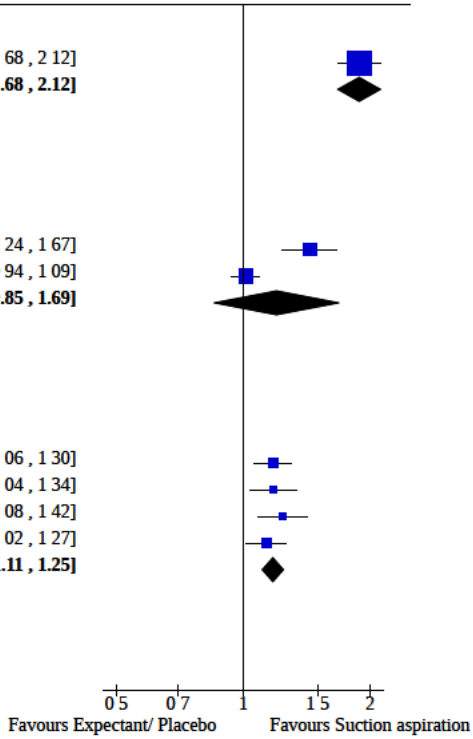
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Complete Miscarriage	7		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1.1 Missed miscarriage	1	616	Risk Ratio (IV, Random, 95% CI)	1.88 [1.68, 2.12]
4.1.2 Incomplete miscarriage	2	300	Risk Ratio (IV, Random, 95% CI)	1.20 [0.85, 1.69]
4.1.3 Mixed population	4	776	Risk Ratio (IV, Random, 95% CI)	1.18 [1.11, 1.25]
4.2 Composite outcome of death or serious complication	5	1485	Risk Ratio (IV, Random, 95% CI)	0.43 [0.12, 1.53]
4.3 Need for unplanned/emergency surgical procedure	4	842	Risk Ratio (IV, Random, 95% CI)	0.51 [0.30, 0.87]
4.4 Pelvic inflammatory disease, sepsis or endometritis	8	1725	Risk Ratio (IV, Random, 95% CI)	1.35 [0.76, 2.41]
4.5 Mean volumes of blood loss (millilitres)	1	352	Mean Difference (IV, Random, 95% CI)	-23.00 [-40.41, -5.59]
4.6 Change in haemoglobin measurements before and after the miscarriage	3	603	Mean Difference (IV, Random, 95% CI)	0.18 [0.10, 0.25]
4.7 Days of bleeding	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.8 Cervical tear	2	492	Risk Ratio (IV, Random, 95% CI)	Not estimable
4.9 Mean duration of hospital stay (days)	1	140	Mean Difference (IV, Random, 95% CI)	0.99 [0.74, 1.24]
4.10 Re-admission to hospital	2	463	Risk Ratio (IV, Random, 95% CI)	0.72 [0.15, 3.41]
4.11 Vomiting	1	111	Risk Ratio (IV, Random, 95% CI)	0.82 [0.19, 3.50]
4.12 Diarrhoea	1	111	Risk Ratio (IV, Random, 95% CI)	1.82 [0.71, 4.67]

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.13 Pyrexia	1	111	Risk Ratio (IV, Random, 95% CI)	3.28 [0.69, 15.57]
4.14 Anxiety score	1	111	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.49, 0.26]
4.15 Depression score	1	111	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.67, 0.08]

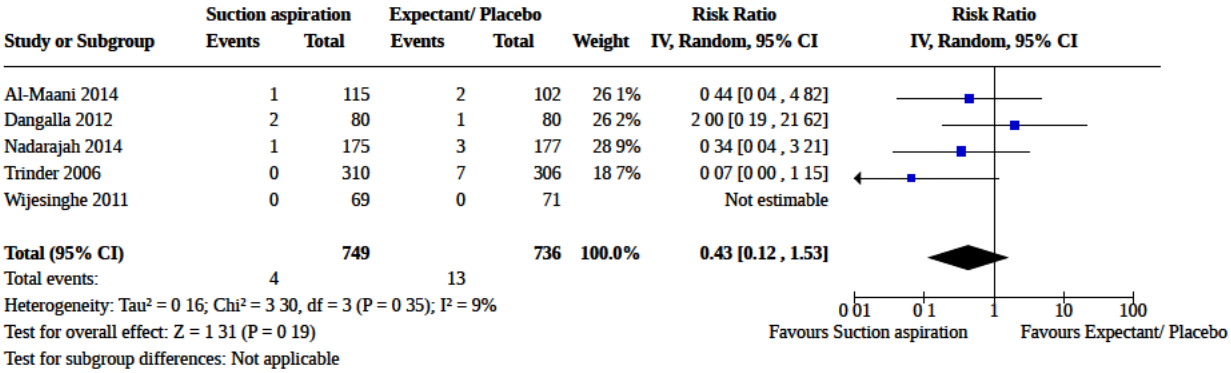
Analysis 4.1. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 1: Complete Miscarriage

Study or Subgroup	Suction aspiration Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.1.1 Missed miscarriage						
Trinder 2006	290	310	152	306	100 0%	1 88 [1 68 , 2 12]
Subtotal (95% CI)		**310**		**306**	**100.0%**	**1.88 [1.68 , 2.12]**
Total events:	290		152			
Heterogeneity: Not applicable						
Test for overall effect: Z = 10 65 (P < 0 00001)						
4.1.2 Incomplete miscarriage						
Dangalla 2012	79	80	55	80	48 2%	1 44 [1 24 , 1 67]
Wijesinghe 2011	66	69	67	71	51 8%	1 01 [0 94 , 1 09]
Subtotal (95% CI)		**149**		**151**	**100.0%**	**1.20 [0.85 , 1.69]**
Total events:	145		122			
Heterogeneity: Tau² = 0 06; Chi² = 16 55, df = 1 (P < 0 0001); I² = 94%						
Test for overall effect: Z = 1 04 (P = 0 30)						
4.1.3 Mixed population						
Al-Maani 2014	110	115	83	102	33 0%	1 18 [1 06 , 1 30]
Karlsen 2001	48	48	39	46	20 5%	1 18 [1 04 , 1 34]
Kong 2013	54	55	46	58	18 0%	1 24 [1 08 , 1 42]
Nadarajah 2014	147	175	131	177	28 4%	1 13 [1 02 , 1 27]
Subtotal (95% CI)		**393**		**383**	**100.0%**	**1.18 [1.11 , 1.25]**
Total events:	359		299			
Heterogeneity: Tau² = 0 00; Chi² = 0 96, df = 3 (P = 0 81); I² = 0%						
Test for overall effect: Z = 5 47 (P < 0 00001)						
Test for subgroup differences: Chi² = 50 65, df = 2 (P < 0 00001), I² = 96 1%						



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 4.2. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 2: Composite outcome of death or serious complication

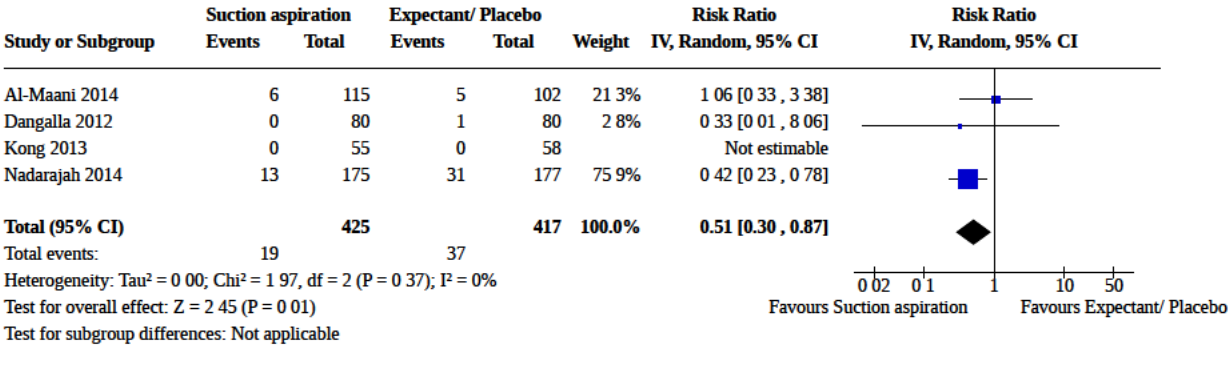


Study or Subgroup	Suction aspiration Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Al-Maani 2014	1	115	2	102	26 1%	0 44 [0 04 , 4 82]
Dangalla 2012	2	80	1	80	26 2%	2 00 [0 19 , 21 62]
Nadarajah 2014	1	175	3	177	28 9%	0 34 [0 04 , 3 21]
Trinder 2006	0	310	7	306	18 7%	0 07 [0 00 , 1 15]
Wijesinghe 2011	0	69	0	71		Not estimable
Total (95% CI)		**749**		**736**	**100.0%**	**0.43 [0.12 , 1.53]**
Total events:	4		13			

Heterogeneity: Tau² = 0 16; Chi² = 3 30, df = 3 (P = 0 35); I² = 9%
Test for overall effect: Z = 1 31 (P = 0 19)
Test for subgroup differences: Not applicable

Risk Ratio IV, Random, 95% CI
0 01 0 1 1 10 100
Favours Suction aspiration Favours Expectant/ Placebo

Analysis 4.3. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 3: Need for unplanned/emergency surgical procedure

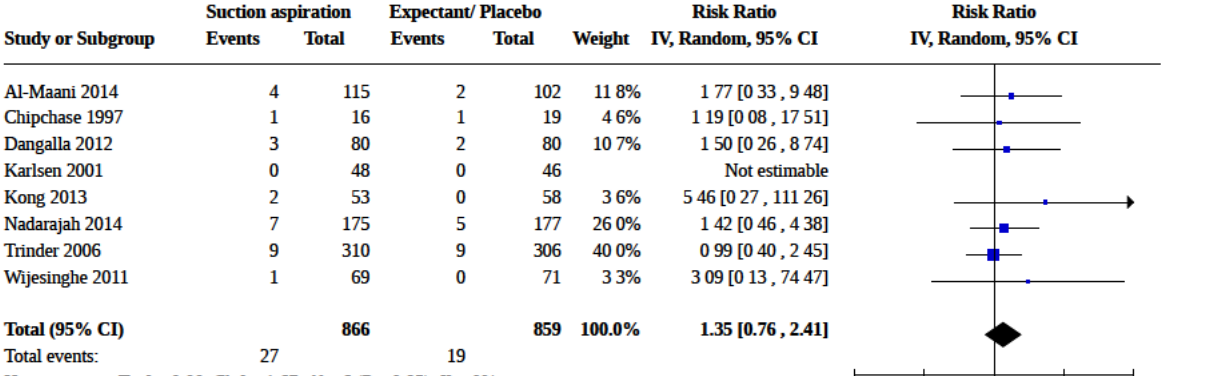


Study or Subgroup	Suction aspiration Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Al-Maani 2014	6	115	5	102	21 3%	1 06 [0 33 , 3 38]
Dangalla 2012	0	80	1	80	2 8%	0 33 [0 01 , 8 06]
Kong 2013	0	55	0	58		Not estimable
Nadarajah 2014	13	175	31	177	75 9%	0 42 [0 23 , 0 78]
Total (95% CI)		**425**		**417**	**100.0%**	**0.51 [0.30 , 0.87]**
Total events:	19		37			

Heterogeneity: Tau² = 0 00; Chi² = 1 97, df = 2 (P = 0 37); I² = 0%
Test for overall effect: Z = 2 45 (P = 0 01)
Test for subgroup differences: Not applicable

Risk Ratio IV, Random, 95% CI
0 02 0 1 1 10 50
Favours Suction aspiration Favours Expectant/ Placebo

Analysis 4.4. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 4: Pelvic inflammatory disease, sepsis or endometritis



Study or Subgroup	Suction aspiration Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Al-Maani 2014	4	115	2	102	11 8%	1 77 [0 33 , 9 48]
Chipchase 1997	1	16	1	19	4 6%	1 19 [0 08 , 17 51]
Dangalla 2012	3	80	2	80	10 7%	1 50 [0 26 , 8 74]
Karlsen 2001	0	48	0	46		Not estimable
Kong 2013	2	53	0	58	3 6%	5 46 [0 27 , 111 26]
Nadarajah 2014	7	175	5	177	26 0%	1 42 [0 46 , 4 38]
Trinder 2006	9	310	9	306	40 0%	0 99 [0 40 , 2 45]
Wijesinghe 2011	1	69	0	71	3 3%	3 09 [0 13 , 74 47]
Total (95% CI)		**866**		**859**	**100.0%**	**1.35 [0.76 , 2.41]**
Total events:	27		19			

Heterogeneity: Tau² = 0 00; Chi² = 1 67, df = 6 (P = 0 95); I² = 0%
Test for overall effect: Z = 1 03 (P = 0 30)
Test for subgroup differences: Not applicable

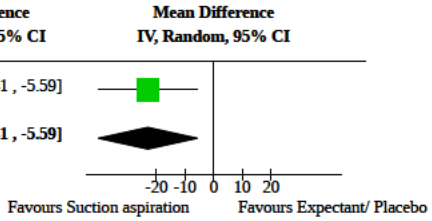
Risk Ratio IV, Random, 95% CI
0 01 0 1 1 10 100
Favours Suction aspiration Favours Expectant/ Placebo

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 4.5. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 5: Mean volumes of blood loss (millilitres)

Study or Subgroup	Suction aspiration Mean	SD	Total	Expectant/ Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nadarajah 2014	148	83.31	175	171	83.31	177	100.0%	-23.00 [-40.41 , -5.59]
Total (95% CI)			**175**			**177**	**100.0%**	**-23.00 [-40.41 , -5.59]**

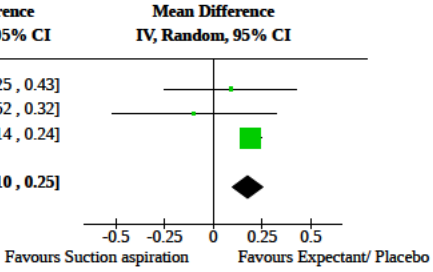
Heterogeneity: Not applicable
Test for overall effect: Z = 2.59 (P = 0.010)
Test for subgroup differences: Not applicable



Analysis 4.6. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 6: Change in haemoglobin measurements before and after the miscarriage

Study or Subgroup	Suction aspiration Mean	SD	Total	Expectant/ Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kong 2013	0.12	0.84	53	0.03	0.98	58	5.0%	0.09 [-0.25 , 0.43]
Nadarajah 2014	0.8	2.01	175	0.9	2.01	177	3.3%	-0.10 [-0.52 , 0.32]
Wijesinghe 2011	0.91	0.12	69	0.72	0.2	71	91.7%	0.19 [0.14 , 0.24]
Total (95% CI)			**297**			**306**	**100.0%**	**0.18 [0.10 , 0.25]**

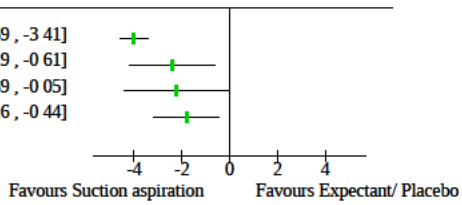
Heterogeneity: Tau² = 0.00; Chi² = 2.10, df = 2 (P = 0.35); I² = 5%
Test for overall effect: Z = 4.47 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.7. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 7: Days of bleeding

Study or Subgroup	Suction aspiration Mean	SD	Total	Expectant/ Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
Al-Maani 2014	7	2 1	115	11	2 3	102	-4 00 [-4 59 , -3 41]
Karlsen 2001	4 8	4 42	48	7 2	4 42	46	-2 40 [-4 19 , -0 61]
Kong 2013	10 73	5 92	53	12 95	5 73	58	-2 22 [-4 39 , -0 05]
Nadarajah 2014	3 5	6 52	175	5 3	6 52	177	-1 80 [-3 16 , -0 44]

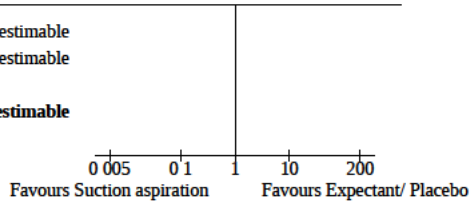
Test for subgroup differences: Not applicable



Analysis 4.8. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 8: Cervical tear

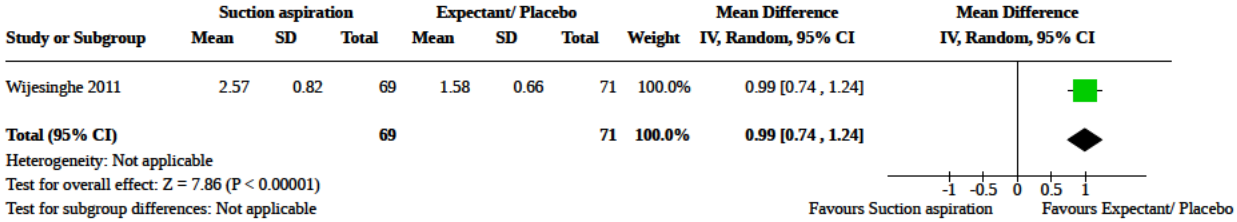
Study or Subgroup	Suction aspiration Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Nadarajah 2014	0	175	0	177		Not estimable
Wijesinghe 2011	0	69	0	71		Not estimable
Total (95% CI)		**244**		**248**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

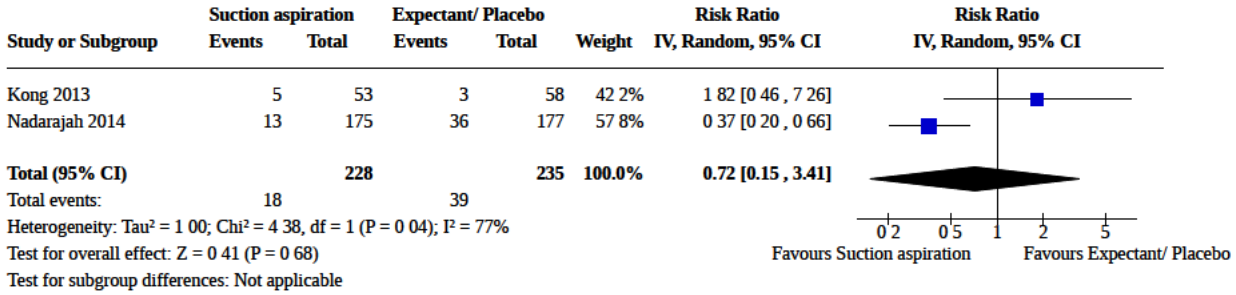


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

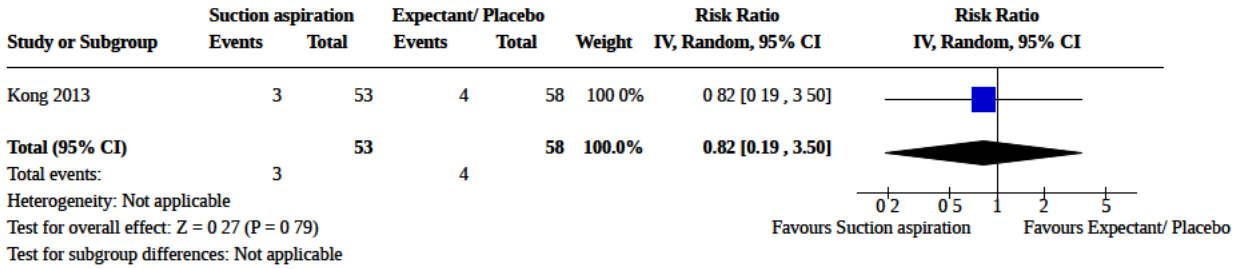
Analysis 4.9. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 9: Mean duration of hospital stay (days)



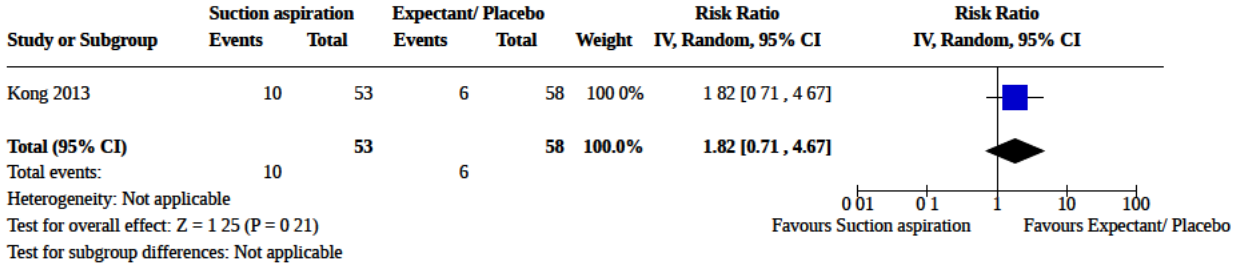
Analysis 4.10. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 10: Re-admission to hospital



Analysis 4.11. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 11: Vomiting

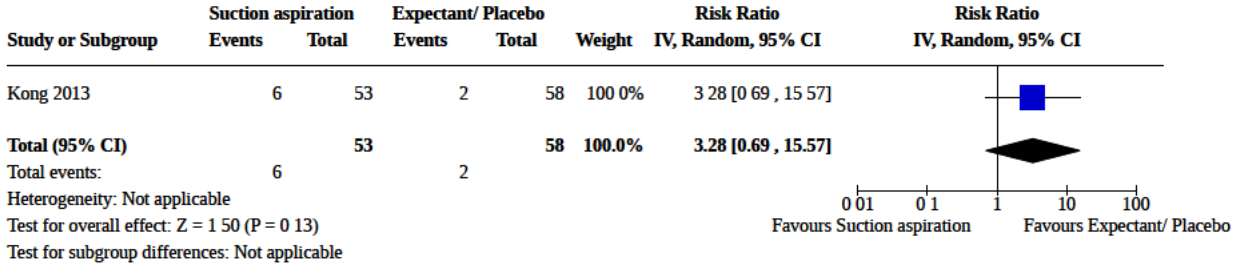


Analysis 4.12. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 12: Diarrhoea

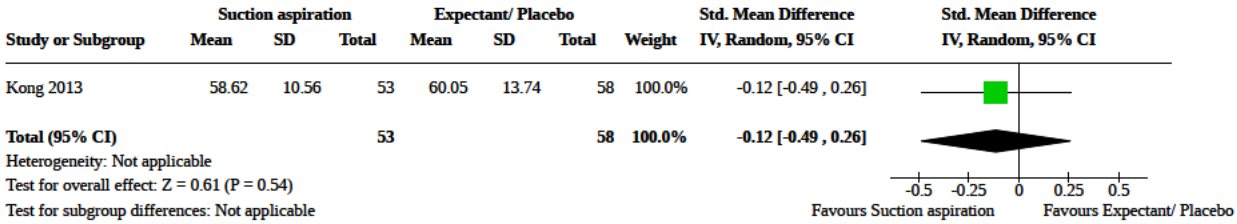


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

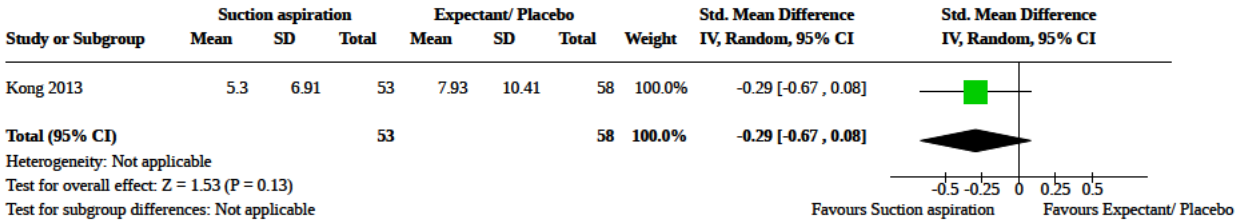
Analysis 4.13. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 13: Pyrexia



Analysis 4.14. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 14: Anxiety score



Analysis 4.15. Comparison 4: Suction aspiration vs Expectant/ Placebo, Outcome 15: Depression score



Comparison 5. Misoprostol vs Mifepristone + Misoprostol

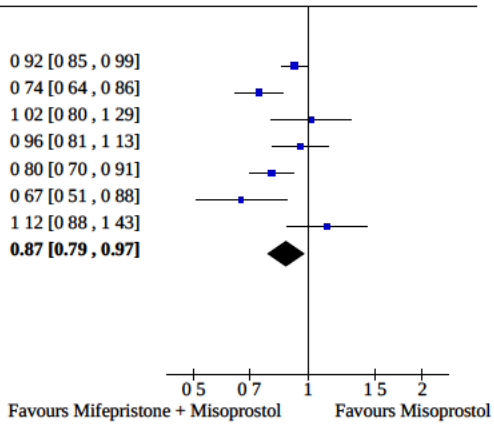
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Complete Miscarriage	7		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1.1 Missed miscarriage	7	1812	Risk Ratio (IV, Random, 95% CI)	0.87 [0.79, 0.97]
5.2 Composite outcome of death or serious complication	7	1822	Risk Ratio (IV, Random, 95% CI)	0.50 [0.20, 1.25]
5.3 Need for unplanned/emergency surgical procedure	6	1527	Risk Ratio (IV, Random, 95% CI)	1.55 [1.22, 1.96]
5.4 Pelvic inflammatory disease, sepsis or endometritis	5	1617	Risk Ratio (IV, Random, 95% CI)	1.02 [0.54, 1.92]
5.5 Change in haemoglobin measurements before and after the miscarriage	1	90	Mean Difference (IV, Random, 95% CI)	0.02 [-0.18, 0.22]

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.6 Days of bleeding	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.7 Re-admission to hospital	1	344	Risk Ratio (IV, Random, 95% CI)	2.30 [1.48, 3.58]
5.8 Nausea	2	570	Risk Ratio (IV, Random, 95% CI)	0.74 [0.39, 1.39]
5.9 Vomiting	1	300	Risk Ratio (IV, Random, 95% CI)	0.57 [0.36, 0.90]
5.10 Diarrhoea	2	570	Risk Ratio (IV, Random, 95% CI)	1.09 [0.83, 1.44]
5.11 Pyrexia	4	685	Risk Ratio (IV, Random, 95% CI)	0.74 [0.34, 1.62]

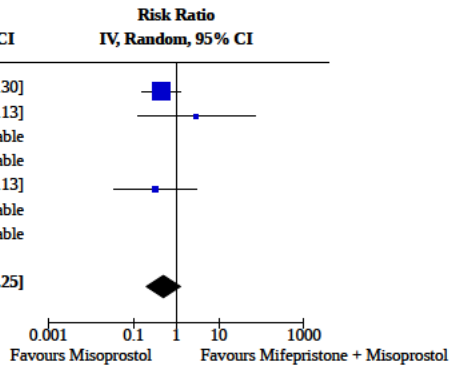
Analysis 5.1. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 1: Complete Miscarriage

Study or Subgroup	Misoprostol Events	Misoprostol Total	Mifepristone + Misoprostol Events	Mifepristone + Misoprostol Total	Weight	Risk Ratio IV, Random, 95% CI
5.1.1 Missed miscarriage						
Chu 2020	266	348	289	348	21 0%	0 92 [0 85 , 0 99]
Hamel 2021	101	172	136	172	16 3%	0 74 [0 64 , 0 86]
Machtinger 2002	25	31	27	34	10 6%	1 02 [0 80 , 1 29]
Machtinger 2004	79	111	70	94	14 9%	0 96 [0 81 , 1 13]
Schreiber 2018	100	149	124	148	17 2%	0 80 [0 70 , 0 91]
Sinha 2018	26	45	39	45	9 2%	0 67 [0 51 , 0 88]
Stockheim 2006	42	57	38	58	10 6%	1 12 [0 88 , 1 43]
Subtotal (95% CI)		**913**		**899**	**100.0%**	**0.87 [0.79 , 0.97]**
Total events:	639		723			
Heterogeneity: Tau² = 0 01; Chi² = 18 52, df = 6 (P = 0 005); I² = 68%						
Test for overall effect: Z = 2 45 (P = 0 01)						
Test for subgroup differences: Not applicable						



Analysis 5.2. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 2: Composite outcome of death or serious complication

Study or Subgroup	Misoprostol Events	Misoprostol Total	Mifepristone + Misoprostol Events	Mifepristone + Misoprostol Total	Weight	Risk Ratio IV, Random, 95% CI
Chu 2020	5	351	11	352	75.6%	0.46 [0.16 , 1.30]
Hamel 2021	1	172	0	172	8.1%	3.00 [0.12 , 73.13]
Machtinger 2002	0	31	0	34		Not estimable
Machtinger 2004	0	111	0	94		Not estimable
Schreiber 2018	1	151	3	149	16.3%	0.33 [0.03 , 3.13]
Sinha 2018	0	45	0	45		Not estimable
Stockheim 2006	0	57	0	58		Not estimable
Total (95% CI)		**918**		**904**	**100.0%**	**0.50 [0.20 , 1.25]**
Total events:	7		14			
Heterogeneity: Tau² = 0.00; Chi² = 1.37, df = 2 (P = 0.50); I² = 0%						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Not applicable						

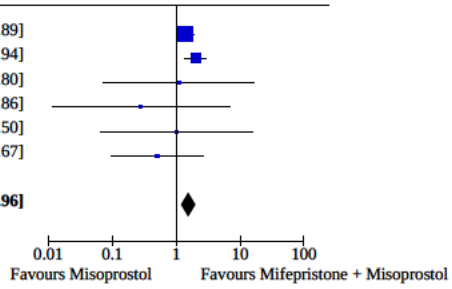


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 5.3. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 3: Need for unplanned/emergency surgical procedure

Study or Subgroup	Misoprostol Events	Misoprostol Total	Mifepristone + Misoprostol Events	Mifepristone + Misoprostol Total	Weight	Risk Ratio IV, Random, 95% CI
Chu 2020	87	353	62	355	60.1%	1.41 [1.06 , 1.89]
Hamel 2021	60	172	30	172	35.8%	2.00 [1.36 , 2.94]
Machtinger 2002	1	31	1	34	0.7%	1.10 [0.07 , 16.80]
Machtinger 2004	0	111	1	94	0.5%	0.28 [0.01 , 6.86]
Sinha 2018	1	45	1	45	0.7%	1.00 [0.06 , 15.50]
Stockheim 2006	2	57	4	58	2.0%	0.51 [0.10 , 2.67]
Total (95% CI)		**769**		**758**	**100.0%**	**1.55 [1.22 , 1.96]**
Total events:	151		99			

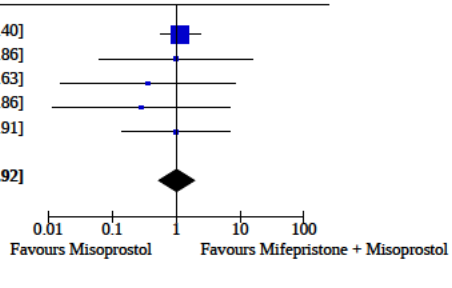
Heterogeneity: Tau² = 0.00; Chi² = 5.08, df = 5 (P = 0.41); I² = 2%
Test for overall effect: Z = 3.61 (P = 0.0003)
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 4: Pelvic inflammatory disease, sepsis or endometritis

Study or Subgroup	Misoprostol Events	Misoprostol Total	Mifepristone + Misoprostol Events	Mifepristone + Misoprostol Total	Weight	Risk Ratio IV, Random, 95% CI
Chu 2020	15	351	13	352	76.1%	1.16 [0.56 , 2.40]
Hamel 2021	1	172	1	172	5.3%	1.00 [0.06 , 15.86]
Machtinger 2002	0	31	1	34	4.0%	0.36 [0.02 , 8.63]
Machtinger 2004	0	111	1	94	4.0%	0.28 [0.01 , 6.86]
Schreiber 2018	2	151	2	149	10.6%	0.99 [0.14 , 6.91]
Total (95% CI)		**816**		**801**	**100.0%**	**1.02 [0.54 , 1.92]**
Total events:	18		18			

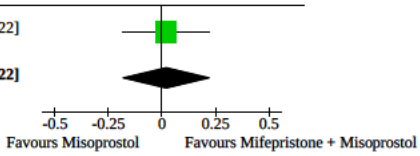
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 4 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable



Analysis 5.5. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 5: Change in haemoglobin measurements before and after the miscarriage

Study or Subgroup	Misoprostol Mean	Misoprostol SD	Misoprostol Total	Mifepristone + Misoprostol Mean	Mifepristone + Misoprostol SD	Mifepristone + Misoprostol Total	Weight	Mean Difference IV, Random, 95% CI
Sinha 2018	0.62	0.49	45	0.6	0.49	45	100.0%	0.02 [-0.18 , 0.22]
Total (95% CI)			**45**			**45**	**100.0%**	**0.02 [-0.18 , 0.22]**

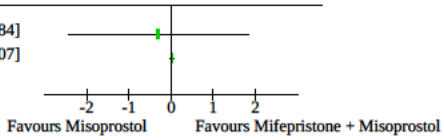
Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable



Analysis 5.6. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 6: Days of bleeding

Study or Subgroup	Misoprostol Mean	Misoprostol SD	Misoprostol Total	Mifepristone + Misoprostol Mean	Mifepristone + Misoprostol SD	Mifepristone + Misoprostol Total	Mean Difference IV, Random, 95% CI
Chu 2020	16	12.6	326	16.3	15.2	330	-0.30 [-2.44 , 1.84]
Sinha 2018	6.22	0.11	45	6.2	0.11	45	0.02 [-0.03 , 0.07]

Test for subgroup differences: Not applicable

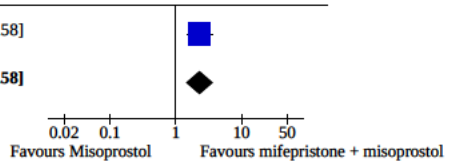


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 5.7. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 7: Re-admission to hospital

Study or Subgroup	Misoprostol Events	Misoprostol Total	Mifepristone + misoprostol Events	Mifepristone + misoprostol Total	Weight	Risk Ratio IV, Random, 95% CI
Hamel 2021	53	172	23	172	100.0%	2.30 [1.48 , 3.58]
Total (95% CI)		**172**		**172**	**100.0%**	**2.30 [1.48 , 3.58]**
Total events:	53		23			

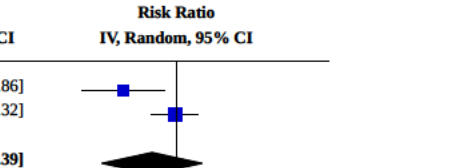
Heterogeneity: Not applicable
Test for overall effect: Z = 3.71 (P = 0.0002)
Test for subgroup differences: Not applicable



Analysis 5.8. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 8: Nausea

Study or Subgroup	Misoprostol Events	Misoprostol Total	Mifepristone + Misoprostol Events	Mifepristone + Misoprostol Total	Weight	Risk Ratio IV, Random, 95% CI
Hamel 2021	18	137	34	133	44.4%	0.51 [0.31 , 0.86]
Schreiber 2018	56	151	56	149	55.6%	0.99 [0.74 , 1.32]
Total (95% CI)		**288**		**282**	**100.0%**	**0.74 [0.39 , 1.39]**
Total events:	74		90			

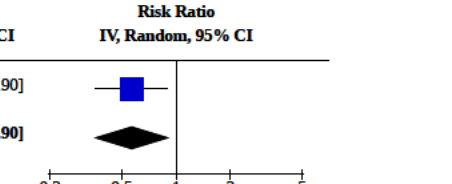
Heterogeneity: Tau² = 0.17; Chi² = 4.60, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 5.9. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 9: Vomiting

Study or Subgroup	Misoprostol Events	Misoprostol Total	Mifepristone + Misoprostol Events	Mifepristone + Misoprostol Total	Weight	Risk Ratio IV, Random, 95% CI
Schreiber 2018	23	151	40	149	100.0%	0.57 [0.36 , 0.90]
Total (95% CI)		**151**		**149**	**100.0%**	**0.57 [0.36 , 0.90]**
Total events:	23		40			

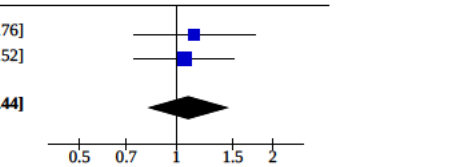
Heterogeneity: Not applicable
Test for overall effect: Z = 2.41 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 5.10. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 10: Diarrhoea

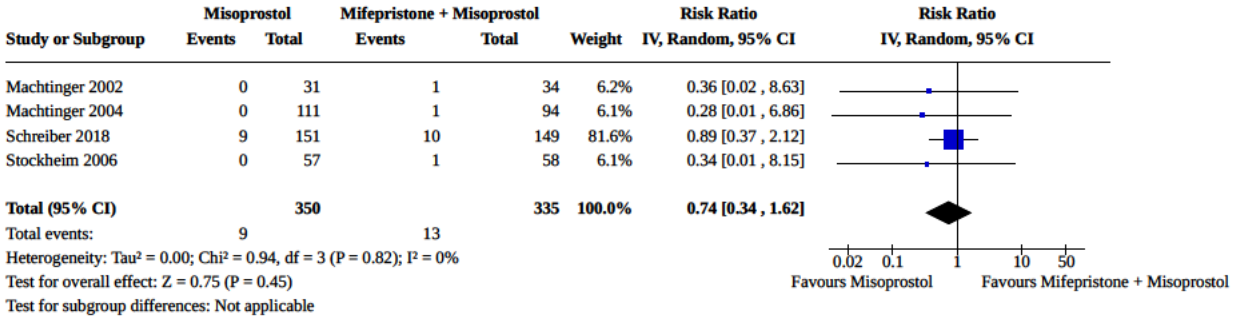
Study or Subgroup	Misoprostol Events	Misoprostol Total	Mifepristone + Misoprostol Events	Mifepristone + Misoprostol Total	Weight	Risk Ratio IV, Random, 95% CI
Hamel 2021	34	137	29	133	40.8%	1.14 [0.74 , 1.76]
Schreiber 2018	44	151	41	149	59.2%	1.06 [0.74 , 1.52]
Total (95% CI)		**288**		**282**	**100.0%**	**1.09 [0.83 , 1.44]**
Total events:	78		70			

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable



Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 5.11. Comparison 5: Misoprostol vs Mifepristone + Misoprostol, Outcome 11: Pyrexia



Comparison 6. Misoprostol vs Dilatation & Curettage

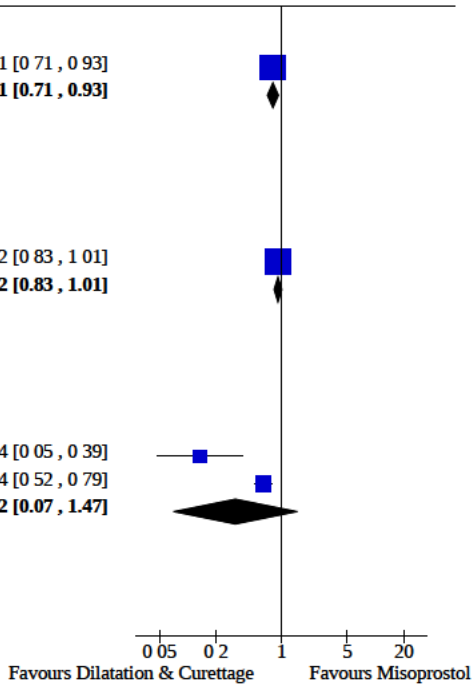
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Complete Miscarriage	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.1.1 Missed miscarriage	1	107	Risk Ratio (IV, Random, 95% CI)	0.81 [0.71, 0.93]
6.1.2 Incomplete miscarriage	1	94	Risk Ratio (IV, Random, 95% CI)	0.92 [0.83, 1.01]
6.1.3 Mixed population	2	154	Risk Ratio (IV, Random, 95% CI)	0.32 [0.07, 1.47]
6.2 Composite outcome of death or serious complication	2	157	Risk Ratio (IV, Random, 95% CI)	1.26 [0.54, 2.97]
6.3 Need for unplanned/emergency surgical procedure	1	94	Risk Ratio (IV, Random, 95% CI)	Not estimable
6.4 Pain score	1	94	Std. Mean Difference (IV, Random, 95% CI)	0.51 [0.10, 0.92]
6.5 Pelvic inflammatory disease, sepsis or endometritis	2	201	Risk Ratio (IV, Random, 95% CI)	2.12 [0.20, 22.64]
6.6 Mean volumes of blood loss (millilitres)	1	104	Mean Difference (IV, Random, 95% CI)	22.30 [4.45, 40.15]
6.7 Days of bleeding	1	94	Mean Difference (IV, Random, 95% CI)	2.60 [1.27, 3.93]
6.8 Cervical tear	1	107	Risk Ratio (IV, Random, 95% CI)	Not estimable
6.9 Re-admission to hospital	1	107	Risk Ratio (IV, Random, 95% CI)	3.17 [0.13, 76.11]
6.10 Vomiting	1	94	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.98]
6.11 Nausea	1	94	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.98]
6.12 Diarrhoea	1	94	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 71.82]

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.13 Depression score	1	215	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.36, 0.18]

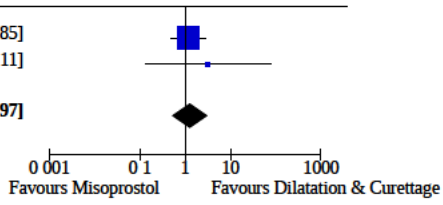
Analysis 6.1. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 1: Complete Miscarriage

Study or Subgroup	Misoprostol Events	Misoprostol Total	Dilatation & Curettage Events	Dilatation & Curettage Total	Weight	Risk Ratio IV, Random, 95% CI
6.1.1 Missed miscarriage						
Shuaib 2013	42	52	55	55	100 0%	0 81 [0 71 , 0 93]
Subtotal (95% CI)		**52**		**55**	**100.0%**	**0.81 [0.71 , 0.93]**
Total events:	42		55			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3 05 (P = 0 002)						
6.1.2 Incomplete miscarriage						
Moodliar 2005	43	47	47	47	100 0%	0 92 [0 83 , 1 01]
Subtotal (95% CI)		**47**		**47**	**100.0%**	**0.92 [0.83 , 1.01]**
Total events:	43		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1 81 (P = 0 07)						
6.1.3 Mixed population						
de Jonge 1995	3	23	26	27	44 2%	0 14 [0 05 , 0 39]
Kyaw 2015	32	50	54	54	55 8%	0 64 [0 52 , 0 79]
Subtotal (95% CI)		**73**		**81**	**100.0%**	**0.32 [0.07 , 1.47]**
Total events:	35		80			
Heterogeneity: Tau² = 1 06; Chi² = 8 02, df = 1 (P = 0 005); I² = 88%						
Test for overall effect: Z = 1 46 (P = 0 14)						
Test for subgroup differences: Chi² = 3 80, df = 2 (P = 0 15), I² = 47 4%						



Analysis 6.2. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 2: Composite outcome of death or serious complication

Study or Subgroup	Misoprostol Events	Misoprostol Total	Dilatation & Curettage Events	Dilatation & Curettage Total	Weight	Risk Ratio IV, Random, 95% CI
de Jonge 1995	7	23	7	27	92 8%	1 17 [0 48 , 2 85]
Shuaib 2013	1	52	0	55	7 2%	3 17 [0 13 , 76 11]
Total (95% CI)		**75**		**82**	**100.0%**	**1.26 [0.54 , 2.97]**
Total events:	8		7			
Heterogeneity: Tau² = 0 00; Chi² = 0 35, df = 1 (P = 0 56); I² = 0%						
Test for overall effect: Z = 0 53 (P = 0 59)						
Test for subgroup differences: Not applicable						

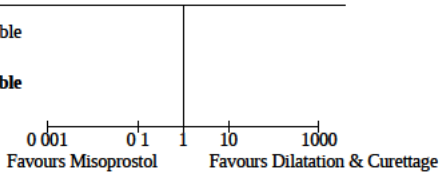


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 6.3. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 3: Need for unplanned/emergency surgical procedure

Study or Subgroup	Misoprostol Events	Misoprostol Total	Dilatation & Curettage Events	Dilatation & Curettage Total	Weight	Risk Ratio IV, Random, 95% CI
Moodliar 2005	0	47	0	47		Not estimable
Total (95% CI)		**47**		**47**		**Not estimable**
Total events:	0		0			

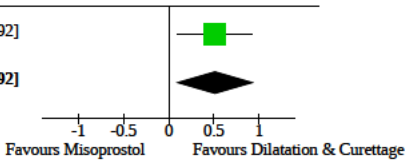
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 4: Pain score

Study or Subgroup	Misoprostol Mean	Misoprostol SD	Misoprostol Total	Dilatation & Curettage Mean	Dilatation & Curettage SD	Dilatation & Curettage Total	Weight	Std. Mean Difference IV, Random, 95% CI
Moodliar 2005	5.6	2.7	47	4.1	3.1	47	100.0%	0.51 [0.10 , 0.92]
Total (95% CI)			**47**			**47**	**100.0%**	**0.51 [0.10 , 0.92]**

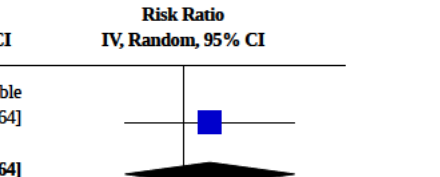
Heterogeneity: Not applicable
Test for overall effect: Z = 2.44 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 6.5. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 5: Pelvic inflammatory disease, sepsis or endometritis

Study or Subgroup	Misoprostol Events	Misoprostol Total	Dilatation & Curettage Events	Dilatation & Curettage Total	Weight	Risk Ratio IV, Random, 95% CI
Moodliar 2005	0	47	0	47		Not estimable
Shuaib 2013	2	52	1	55	100 0%	2 12 [0 20 , 22 64]
Total (95% CI)		**99**		**102**	**100.0%**	**2.12 [0.20 , 22.64]**
Total events:	2		1			

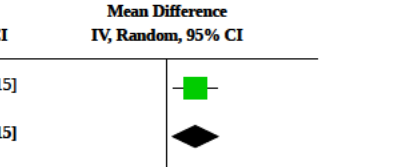
Heterogeneity: Not applicable
Test for overall effect: Z = 0 62 (P = 0 54)
Test for subgroup differences: Not applicable



Analysis 6.6. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 6: Mean volumes of blood loss (millilitres)

Study or Subgroup	Misoprostol Mean	Misoprostol SD	Misoprostol Total	Dilatation & Curettage Mean	Dilatation & Curettage SD	Dilatation & Curettage Total	Weight	Mean Difference IV, Random, 95% CI
Kyaw 2015	77.5	46.4	50	55.2	46.4	54	100.0%	22.30 [4.45 , 40.15]
Total (95% CI)			**50**			**54**	**100.0%**	**22.30 [4.45 , 40.15]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Not applicable

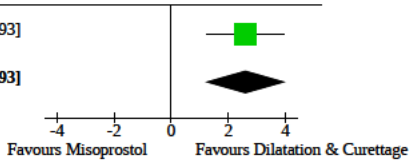


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 6.7. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 7: Days of bleeding

Study or Subgroup	Misoprostol Mean	SD	Total	Dilatation & Curettage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Moodliar 2005	7	3.4	47	4.4	3.2	47	100.0%	2.60 [1.27 , 3.93]
Total (95% CI)			**47**			**47**	**100.0%**	**2.60 [1.27 , 3.93]**

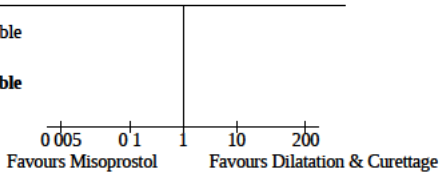
Heterogeneity: Not applicable
Test for overall effect: Z = 3.82 (P = 0.0001)
Test for subgroup differences: Not applicable



Analysis 6.8. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 8: Cervical tear

Study or Subgroup	Misoprostol Events	Total	Dilatation & Curettage Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Shuaib 2013	0	52	0	55		Not estimable
Total (95% CI)		**52**		**55**		**Not estimable**
Total events:	0		0			

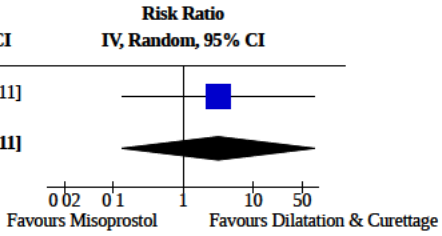
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 6.9. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 9: Re-admission to hospital

Study or Subgroup	Misoprostol Events	Total	Dilatation & Curettage Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Shuaib 2013	1	52	0	55	100 0%	3 17 [0 13 , 76 11]
Total (95% CI)		**52**		**55**	**100.0%**	**3.17 [0.13 , 76.11]**
Total events:	1		0			

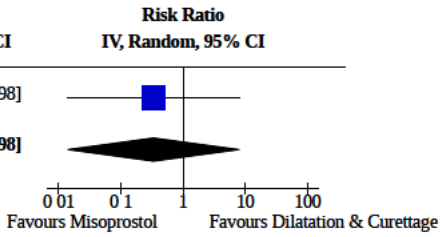
Heterogeneity: Not applicable
Test for overall effect: Z = 0 71 (P = 0 48)
Test for subgroup differences: Not applicable



Analysis 6.10. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 10: Vomiting

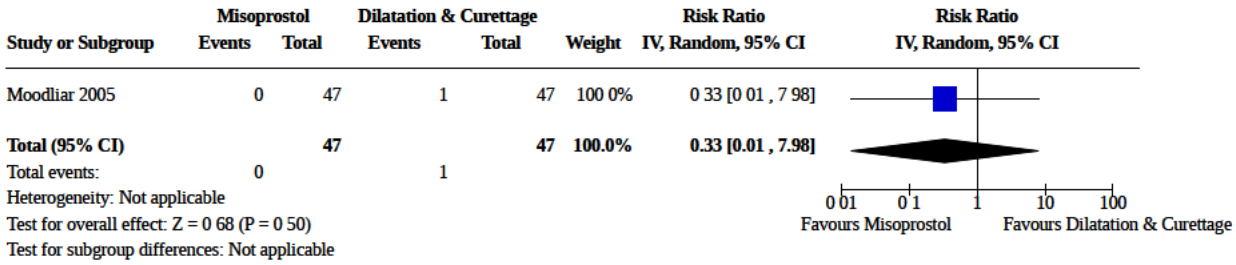
Study or Subgroup	Misoprostol Events	Total	Dilatation & Curettage Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Moodliar 2005	0	47	1	47	100 0%	0 33 [0 01 , 7 98]
Total (95% CI)		**47**		**47**	**100.0%**	**0.33 [0.01 , 7.98]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0 68 (P = 0 50)
Test for subgroup differences: Not applicable

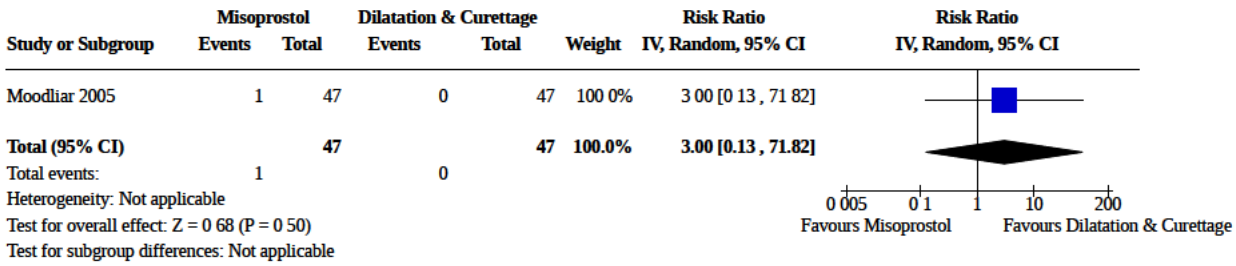


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

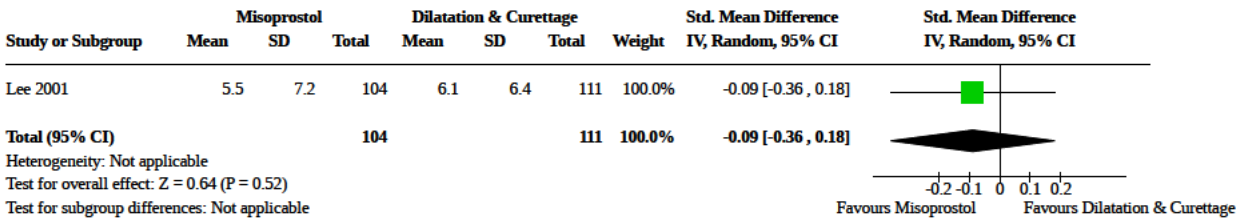
Analysis 6.11. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 11: Nausea



Analysis 6.12. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 12: Diarrhoea



Analysis 6.13. Comparison 6: Misoprostol vs Dilatation & Curettage, Outcome 13: Depression score

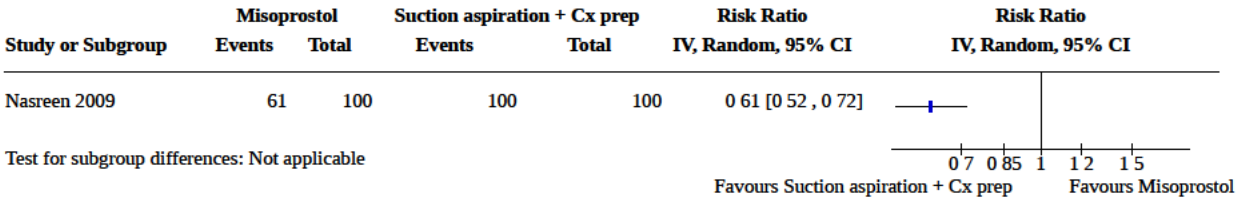


Comparison 7. Misoprostol vs Suction aspiration + Cervical preparation

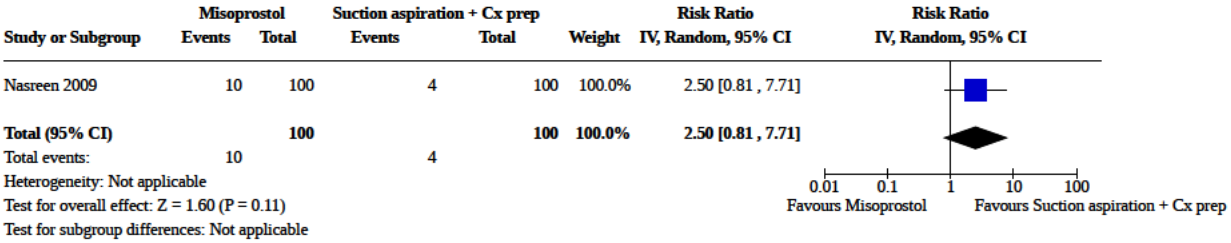
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Complete Miscarriage	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7.2 Pyrexia	1	200	Risk Ratio (IV, Random, 95% CI)	2.50 [0.81, 7.71]

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 7.1. Comparison 7: Misoprostol vs Suction aspiration + Cervical preparation, Outcome 1: Complete Miscarriage



Analysis 7.2. Comparison 7: Misoprostol vs Suction aspiration + Cervical preparation, Outcome 2: Pyrexia



Comparison 8. Misoprostol vs Expectant/ Placebo

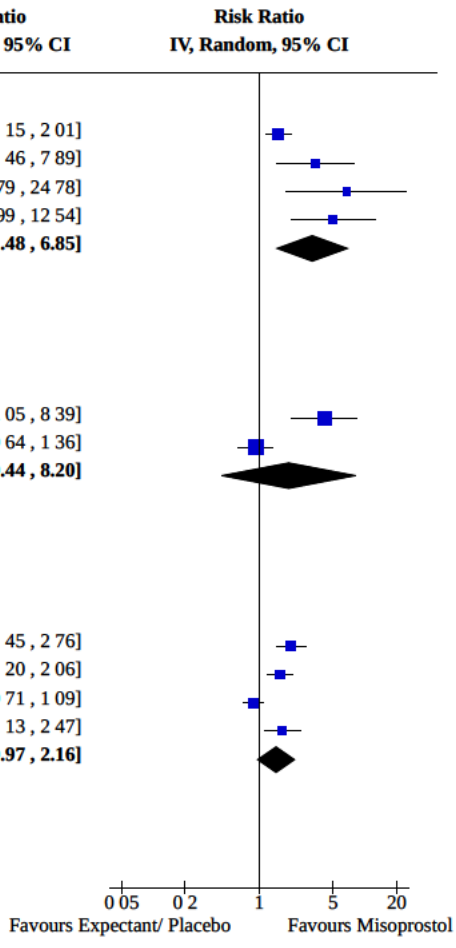
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Complete Miscarriage	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.1.1 Missed miscarriage	4	322	Risk Ratio (IV, Random, 95% CI)	3.18 [1.48, 6.85]
8.1.2 Incomplete miscarriage	2	108	Risk Ratio (IV, Random, 95% CI)	1.91 [0.44, 8.20]
8.1.3 Mixed population	4	408	Risk Ratio (IV, Random, 95% CI)	1.45 [0.97, 2.16]
8.2 Composite outcome of death or serious complication	6	548	Risk Ratio (IV, Random, 95% CI)	0.96 [0.06, 15.08]
8.3 Need for unplanned/emergency surgical procedure	5	437	Risk Ratio (IV, Random, 95% CI)	0.67 [0.23, 1.95]
8.4 Pain score	3	262	Std. Mean Difference (IV, Random, 95% CI)	0.33 [0.08, 0.57]
8.5 Pelvic inflammatory disease, sepsis or endometritis	6	615	Risk Ratio (IV, Random, 95% CI)	1.84 [0.35, 9.68]
8.6 Change in haemoglobin measurements before and after the miscarriage	2	167	Mean Difference (IV, Random, 95% CI)	0.15 [-0.21, 0.52]
8.7 Days of bleeding	3		Mean Difference (IV, Random, 95% CI)	Subtotals only

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.8 Mean duration of hospital stay (days)	1	184	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.19, -0.01]
8.9 Re-admission to hospital	3	335	Risk Ratio (IV, Random, 95% CI)	1.25 [0.46, 3.35]
8.10 Nausea	5	389	Risk Ratio (IV, Random, 95% CI)	1.15 [0.93, 1.42]
8.11 Vomiting	6	506	Risk Ratio (IV, Random, 95% CI)	1.37 [0.75, 2.52]
8.12 Diarrhoea	7	560	Risk Ratio (IV, Random, 95% CI)	1.69 [1.05, 2.73]
8.13 Pyrexia	3	275	Risk Ratio (IV, Random, 95% CI)	4.03 [1.16, 13.97]
8.14 Anxiety score	1	117	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.51, 0.22]
8.15 Depression score	1	117	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.29, 0.44]

Analysis 8.1. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 1: Complete Miscarriage

Study or Subgroup	Misoprostol Events	Misoprostol Total	Expectant/ Placebo Events	Expectant/ Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
8.1.1 Missed miscarriage						
Fernlund 2018	62	94	39	90	34 1%	1 52 [1 15 , 2 01]
Kovavisarach 2002	17	27	5	27	24 9%	3 40 [1 46 , 7 89]
Lister 2005	15	18	2	16	17 4%	6 67 [1 79 , 24 78]
Wood 2002	20	25	4	25	23 6%	5 00 [1 99 , 12 54]
Subtotal (95% CI)		**164**		**158**	**100.0%**	**3.18 [1.48 , 6.85]**
Total events:	114		50			
Heterogeneity: Tau² = 0 43; Chi² = 12 05, df = 3 (P = 0 007); I² = 75%						
Test for overall effect: Z = 2 96 (P = 0 003)						
8.1.2 Incomplete miscarriage						
Abdelaleem 2020	29	42	7	42	47 9%	4 14 [2 05 , 8 39]
Shelley 2005	8	10	12	14	52 1%	0 93 [0 64 , 1 36]
Subtotal (95% CI)		**52**		**56**	**100.0%**	**1.91 [0.44 , 8.20]**
Total events:	37		19			
Heterogeneity: Tau² = 1 03; Chi² = 13 33, df = 1 (P = 0 0003); I² = 92%						
Test for overall effect: Z = 0 87 (P = 0 39)						
8.1.3 Mixed population						
Bagratee 2004	46	52	23	52	24 5%	2 00 [1 45 , 2 76]
Blohm 2005	52	64	32	62	25 8%	1 57 [1 20 , 2 06]
Kong 2013	42	60	46	58	26 9%	0 88 [0 71 , 1 09]
Ngai 2001	25	30	15	30	22 8%	1 67 [1 13 , 2 47]
Subtotal (95% CI)		**206**		**202**	**100.0%**	**1.45 [0.97 , 2.16]**
Total events:	165		116			
Heterogeneity: Tau² = 0 14; Chi² = 23 31, df = 3 (P < 0 0001); I² = 87%						
Test for overall effect: Z = 1 81 (P = 0 07)						
Test for subgroup differences: Chi² = 3 21, df = 2 (P = 0 20), I² = 37 7%						

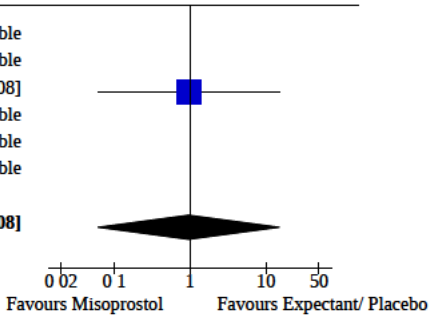


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 8.2. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 2: Composite outcome of death or serious complication

Study or Subgroup	Misoprostol Events	Misoprostol Total	Expectant/ Placebo Events	Expectant/ Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bagratee 2004	0	52	0	52		Not estimable
Blohm 2005	0	64	0	62		Not estimable
Fernlund 2018	1	94	1	90	100 0%	0 96 [0 06 , 15 08]
Ngai 2001	0	30	0	30		Not estimable
Shelley 2005	0	10	0	14		Not estimable
Wood 2002	0	25	0	25		Not estimable
Total (95% CI)		**275**		**273**	**100.0%**	**0.96 [0.06 , 15.08]**
Total events:	1		1			

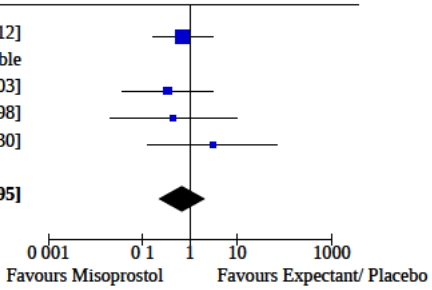
Heterogeneity: Not applicable
Test for overall effect: Z = 0 03 (P = 0 98)
Test for subgroup differences: Not applicable



Analysis 8.3. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 3: Need for unplanned/emergency surgical procedure

Study or Subgroup	Misoprostol Events	Misoprostol Total	Expectant/ Placebo Events	Expectant/ Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Fernlund 2018	3	94	4	90	53 1%	0 72 [0 17 , 3 12]
Kong 2013	0	59	0	58		Not estimable
Ngai 2001	1	30	3	30	23 5%	0 33 [0 04 , 3 03]
Shelley 2005	0	11	1	15	11 8%	0 44 [0 02 , 9 98]
Wood 2002	1	25	0	25	11 5%	3 00 [0 13 , 70 30]
Total (95% CI)		**219**		**218**	**100.0%**	**0.67 [0.23 , 1.95]**
Total events:	5		8			

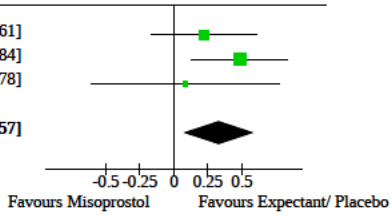
Heterogeneity: Tau² = 0 00; Chi² = 1 33, df = 3 (P = 0 72); I² = 0%
Test for overall effect: Z = 0 74 (P = 0 46)
Test for subgroup differences: Not applicable



Analysis 8.4. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 4: Pain score

Study or Subgroup	Misoprostol Mean	Misoprostol SD	Misoprostol Total	Expectant/ Placebo Mean	Expectant/ Placebo SD	Expectant/ Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bagratee 2004	6	2.7	52	5.4	2.7	52	40.1%	0.22 [-0.17 , 0.61]
Blohm 2005	60.4	31	64	43.8	37.1	62	47.5%	0.48 [0.13 , 0.84]
Lister 2005	5.6	4.57	16	5.2	4.57	16	12.4%	0.09 [-0.61 , 0.78]
Total (95% CI)			**132**			**130**	**100.0%**	**0.33 [0.08 , 0.57]**

Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 2.64 (P = 0.008)
Test for subgroup differences: Not applicable

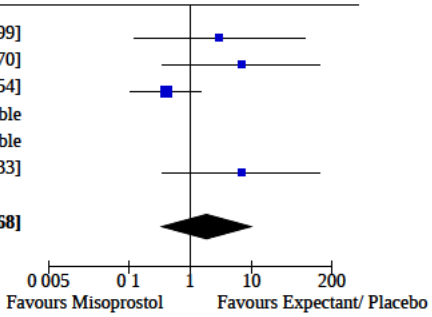


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 8.5. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 5: Pelvic inflammatory disease, sepsis or endometritis

Study or Subgroup	Misoprostol Events	Misoprostol Total	Expectant/ Placebo Events	Expectant/ Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bagratee 2004	1	52	0	52	18 3%	3 00 [0 13 , 71 99]
Blohm 2005	3	64	0	62	20 2%	6 78 [0 36 , 128 70]
Fernlund 2018	3	94	7	90	41 2%	0 41 [0 11 , 1 54]
Kong 2013	0	59	0	58		Not estimable
Ngai 2001	0	30	0	30		Not estimable
Shelley 2005	2	10	0	14	20 3%	6 82 [0 36 , 128 33]
Total (95% CI)		**309**		**306**	**100.0%**	**1.84 [0.35 , 9.68]**
Total events:	9		7			

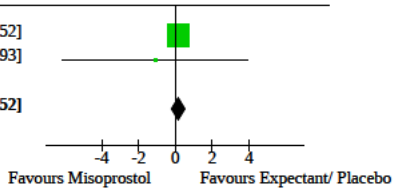
Heterogeneity: Tau² = 1 29; Chi² = 5 47, df = 3 (P = 0 14); I² = 45%
Test for overall effect: Z = 0 72 (P = 0 47)
Test for subgroup differences: Not applicable



Analysis 8.6. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 6: Change in haemoglobin measurements before and after the miscarriage

Study or Subgroup	Misoprostol Mean	Misoprostol SD	Misoprostol Total	Expectant/ Placebo Mean	Expectant/ Placebo SD	Expectant/ Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Kong 2013	0.19	1.03	59	0.03	0.98	58	99.5%	0.16 [-0.20 , 0.52]
Wood 2002	3.2	7.9	25	4.3	10.1	25	0.5%	-1.10 [-6.13 , 3.93]
Total (95% CI)			**84**			**83**	**100.0%**	**0.15 [-0.21 , 0.52]**

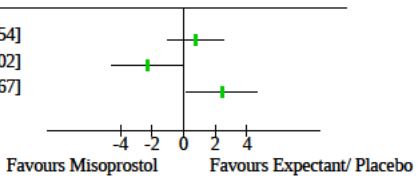
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 8.7. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 7: Days of bleeding

Study or Subgroup	Misoprostol Mean	Misoprostol SD	Misoprostol Total	Expectant/ Placebo Mean	Expectant/ Placebo SD	Expectant/ Placebo Total	Mean Difference IV, Random, 95% CI
Bagratee 2004	11 65	4 4	52	10 88	4 78	52	0 77 [-1 00 , 2 54]
Fernlund 2018	12 7	6 6	91	15	8 2	77	-2 30 [-4 58 , -0 02]
Kong 2013	15 38	6 63	59	12 95	5 73	58	2 43 [0 19 , 4 67]

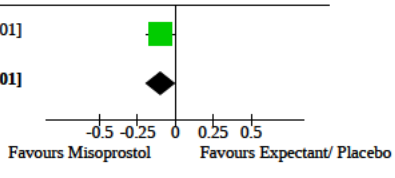
Test for subgroup differences: Not applicable



Analysis 8.8. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 8: Mean duration of hospital stay (days)

Study or Subgroup	Misoprostol Mean	Misoprostol SD	Misoprostol Total	Expectant/ Placebo Mean	Expectant/ Placebo SD	Expectant/ Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Fernlund 2018	0	0.2	94	0.1	0.4	90	100.0%	-0.10 [-0.19 , -0.01]
Total (95% CI)			**94**			**90**	**100.0%**	**-0.10 [-0.19 , -0.01]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.13 (P = 0.03)
Test for subgroup differences: Not applicable

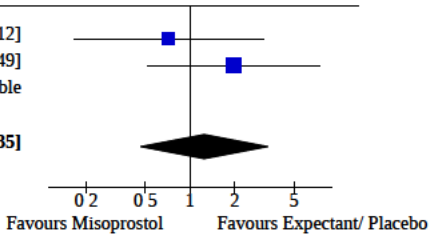


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 8.9. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 9: Re-admission to hospital

Study or Subgroup	Misoprostol Events	Misoprostol Total	Expectant/ Placebo Events	Expectant/ Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Fernlund 2018	3	94	4	90	45 3%	0 72 [0 17 , 3 12]
Kong 2013	6	59	3	58	54 7%	1 97 [0 52 , 7 49]
Lister 2005	0	18	0	16		Not estimable
Total (95% CI)		**171**		**164**	**100.0%**	**1.25 [0.46 , 3.35]**
Total events:	9		7			

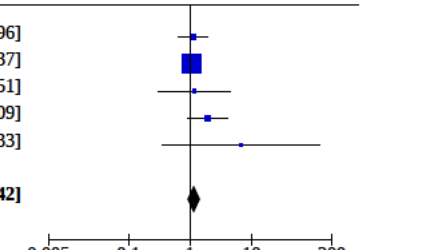
Heterogeneity: Tau² = 0 00; Chi² = 0 99, df = 1 (P = 0 32); I² = 0%
Test for overall effect: Z = 0 43 (P = 0 66)
Test for subgroup differences: Not applicable



Analysis 8.10. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 10: Nausea

Study or Subgroup	Misoprostol Events	Misoprostol Total	Expectant/ Placebo Events	Expectant/ Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bagratee 2004	18	52	16	52	14 7%	1 13 [0 65 , 1 96]
Fernlund 2018	57	91	45	77	74 2%	1 07 [0 84 , 1 37]
Lister 2005	4	18	3	16	2 5%	1 19 [0 31 , 4 51]
Ngai 2001	14	30	7	29	8 0%	1 93 [0 91 , 4 09]
Shelley 2005	2	10	0	14	0 5%	6 82 [0 36 , 128 33]
Total (95% CI)		**201**		**188**	**100.0%**	**1.15 [0.93 , 1.42]**
Total events:	95		71			

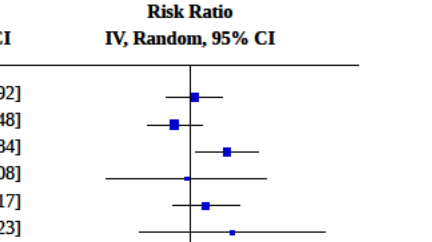
Heterogeneity: Tau² = 0 00; Chi² = 3 58, df = 4 (P = 0 47); I² = 0%
Test for overall effect: Z = 1 26 (P = 0 21)
Test for subgroup differences: Not applicable



Analysis 8.11. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 11: Vomiting

Study or Subgroup	Misoprostol Events	Misoprostol Total	Expectant/ Placebo Events	Expectant/ Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bagratee 2004	8	52	7	52	24 8%	1 14 [0 45 , 2 92]
Fernlund 2018	7	91	10	77	25 5%	0 59 [0 24 , 1 48]
Kong 2013	14	59	4	58	21 6%	3 44 [1 20 , 9 84]
Lister 2005	1	18	1	16	4 7%	0 89 [0 06 , 13 08]
Ngai 2001	7	30	4	29	19 9%	1 69 [0 55 , 5 17]
Shelley 2005	1	10	0	14	3 6%	4 09 [0 18 , 91 23]
Total (95% CI)		**260**		**246**	**100.0%**	**1.37 [0.75 , 2.52]**
Total events:	38		26			

Heterogeneity: Tau² = 0 16; Chi² = 7 00, df = 5 (P = 0 22); I² = 29%
Test for overall effect: Z = 1 02 (P = 0 31)
Test for subgroup differences: Not applicable

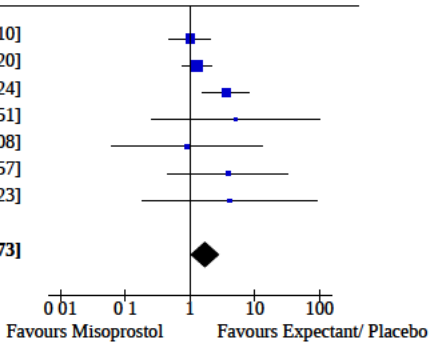


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 8.12. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 12: Diarrhoea

Study or Subgroup	Misoprostol Events	Misoprostol Total	Expectant/ Placebo Events	Expectant/ Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bagratee 2004	11	52	11	52	26 4%	1 00 [0 48 , 2 10]
Fernlund 2018	26	91	17	77	38 1%	1 29 [0 76 , 2 20]
Kong 2013	22	59	6	58	22 9%	3 60 [1 58 , 8 24]
Kovavisarach 2002	2	27	0	27	2 5%	5 00 [0 25 , 99 51]
Lister 2005	1	18	1	16	3 1%	0 89 [0 06 , 13 08]
Ngai 2001	4	30	1	29	4 7%	3 87 [0 46 , 32 57]
Shelley 2005	1	10	0	14	2 3%	4 09 [0 18 , 91 23]
Total (95% CI)		**287**		**273**	**100.0%**	**1.69 [1.05 , 2.73]**
Total events:	67		36			

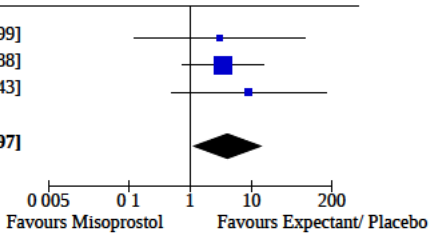
Heterogeneity: Tau² = 0 08; Chi² = 7 61, df = 6 (P = 0 27); I² = 21%
Test for overall effect: Z = 2 14 (P = 0 03)
Test for subgroup differences: Not applicable



Analysis 8.13. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 13: Pyrexia

Study or Subgroup	Misoprostol Events	Misoprostol Total	Expectant/ Placebo Events	Expectant/ Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bagratee 2004	1	52	0	52	15 3%	3 00 [0 13 , 71 99]
Kong 2013	7	59	2	58	66 0%	3 44 [0 75 , 15 88]
Kovavisarach 2002	4	27	0	27	18 7%	9 00 [0 51 , 159 43]
Total (95% CI)		**138**		**137**	**100.0%**	**4.03 [1.16 , 13.97]**
Total events:	12		2			

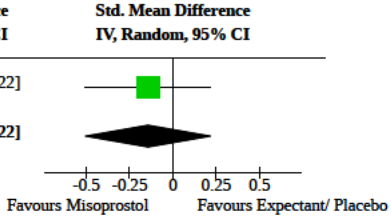
Heterogeneity: Tau² = 0 00; Chi² = 0 37, df = 2 (P = 0 83); I² = 0%
Test for overall effect: Z = 2 20 (P = 0 03)
Test for subgroup differences: Not applicable



Analysis 8.14. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 14: Anxiety score

Study or Subgroup	Misoprostol Mean	Misoprostol SD	Misoprostol Total	Expectant/ Placebo Mean	Expectant/ Placebo SD	Expectant/ Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kong 2013	58.08	13.57	59	60.05	13.74	58	100.0%	-0.14 [-0.51 , 0.22]
Total (95% CI)			**59**			**58**	**100.0%**	**-0.14 [-0.51 , 0.22]**

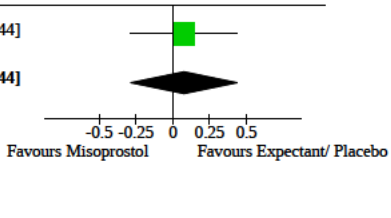
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 8.15. Comparison 8: Misoprostol vs Expectant/ Placebo, Outcome 15: Depression score

Study or Subgroup	Misoprostol Mean	Misoprostol SD	Misoprostol Total	Expectant/ Placebo Mean	Expectant/ Placebo SD	Expectant/ Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kong 2013	8.75	11.05	59	7.93	10.41	58	100.0%	0.08 [-0.29 , 0.44]
Total (95% CI)			**59**			**58**	**100.0%**	**0.08 [-0.29 , 0.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable



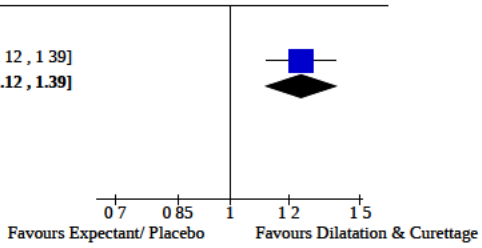
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Comparison 9. Dilatation & Curettage vs Expectant/ Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Complete Miscarriage	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.1.1 Incomplete miscarriage	1	155	Risk Ratio (IV, Random, 95% CI)	1.25 [1.12, 1.39]
9.2 Pelvic inflammatory disease, sepsis or endometritis	1	155	Risk Ratio (IV, Random, 95% CI)	3.30 [0.82, 13.28]
9.3 Days of bleeding	1	155	Mean Difference (IV, Random, 95% CI)	-1.26 [-2.27, -0.25]

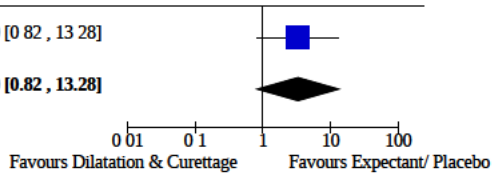
Analysis 9.1. Comparison 9: Dilatation & Curettage vs Expectant/ Placebo, Outcome 1: Complete Miscarriage

Study or Subgroup	Dilatation & Curettage Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
9.1.1 Incomplete miscarriage						
Nielsen 1995	51	52	81	103	100 0%	1 25 [1 12 , 1 39]
Subtotal (95% CI)		**52**		**103**	**100.0%**	**1.25 [1.12 , 1.39]**
Total events:	51		81			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4 02 (P < 0 0001)						
Test for subgroup differences: Not applicable						



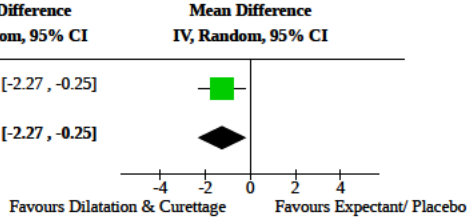
Analysis 9.2. Comparison 9: Dilatation & Curettage vs Expectant/ Placebo, Outcome 2: Pelvic inflammatory disease, sepsis or endometritis

Study or Subgroup	Dilatation & Curettage Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Nielsen 1995	5	52	3	103	100 0%	3 30 [0 82 , 13 28]
Total (95% CI)		**52**		**103**	**100.0%**	**3.30 [0.82 , 13.28]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1 68 (P = 0 09)						
Test for subgroup differences: Not applicable						



Analysis 9.3. Comparison 9: Dilatation & Curettage vs Expectant/ Placebo, Outcome 3: Days of bleeding

Study or Subgroup	Dilatation & Curettage Mean	SD	Total	Expectant/ Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nielsen 1995	7.53	3.06	52	8.79	3.01	103	100.0%	-1.26 [-2.27 , -0.25]
Total (95% CI)			**52**			**103**	**100.0%**	**-1.26 [-2.27 , -0.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.43 (P = 0.01)								
Test for subgroup differences: Not applicable								



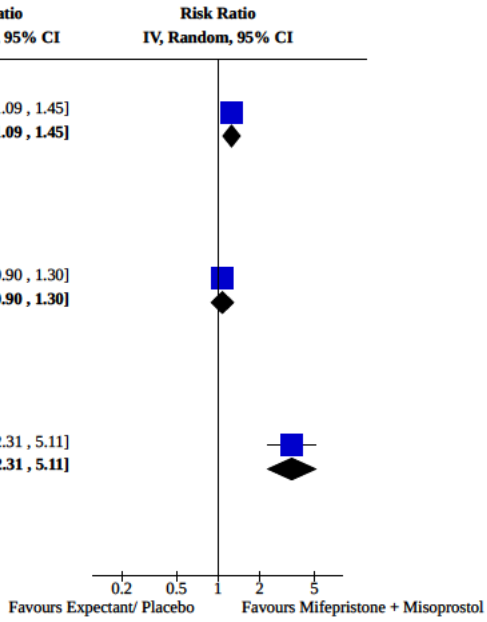
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Comparison 10. Mifepristone + Misoprostol vs Expectant/ Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Complete Miscarriage	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
10.1.1 Missed miscarriage	1	614	Risk Ratio (IV, Random, 95% CI)	1.25 [1.09, 1.45]
10.1.2 Incomplete miscarriage	1	122	Risk Ratio (IV, Random, 95% CI)	1.08 [0.90, 1.30]
10.1.3 Mixed population	1	174	Risk Ratio (IV, Random, 95% CI)	3.44 [2.31, 5.11]
10.2 Composite outcome of death or serious complication	2	788	Risk Ratio (IV, Random, 95% CI)	0.43 [0.11, 1.63]
10.3 Need for unplanned/emergency surgical procedure	2	296	Risk Ratio (IV, Random, 95% CI)	0.32 [0.11, 0.90]
10.4 Pain score	1	122	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.21, 0.50]
10.5 Pelvic inflammatory disease, sepsis or endometritis	2	736	Risk Ratio (IV, Random, 95% CI)	0.73 [0.30, 1.80]
10.6 Days of bleeding	1	122	Mean Difference (IV, Random, 95% CI)	0.70 [-0.43, 1.83]
10.7 Pyrexia	1	174	Risk Ratio (IV, Random, 95% CI)	0.32 [0.01, 7.71]

Analysis 10.1. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 1: Complete Miscarriage

Study or Subgroup	Mifepristone + Misoprostol Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
10.1.1 Missed miscarriage						
Trinder 2006	192	308	152	306	100.0%	1.25 [1.09 , 1.45]
Subtotal (95% CI)		**308**		**306**	**100.0%**	**1.25 [1.09 , 1.45]**
Total events:	192		152			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.13 (P = 0.002)						
10.1.2 Incomplete miscarriage						
Nielsen 1999	49	60	47	62	100.0%	1.08 [0.90 , 1.30]
Subtotal (95% CI)		**60**		**62**	**100.0%**	**1.08 [0.90 , 1.30]**
Total events:	49		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
10.1.3 Mixed population						
Torre 2012	72	89	20	85	100.0%	3.44 [2.31 , 5.11]
Subtotal (95% CI)		**89**		**85**	**100.0%**	**3.44 [2.31 , 5.11]**
Total events:	72		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.11 (P < 0.00001)						
Test for subgroup differences: Chi² = 27.29, df = 2 (P < 0.00001), I² = 92.7%						

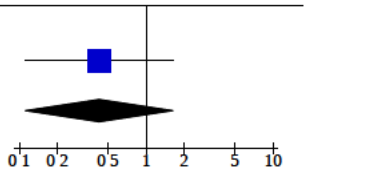


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 10.2. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 2: Composite outcome of death or serious complication

Study or Subgroup	Mifepristone + Misoprostol Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Torre 2012	0	89	0	85		Not estimable
Trinder 2006	3	308	7	306	100 0%	0 43 [0 11 , 1 63]
Total (95% CI)		**397**		**391**	**100.0%**	**0.43 [0.11 , 1.63]**
Total events:	3		7			

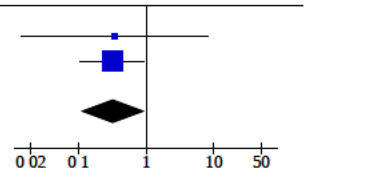
Heterogeneity: Not applicable
Test for overall effect: Z = 1 25 (P = 0 21)
Test for subgroup differences: Not applicable



Analysis 10.3. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 3: Need for unplanned/emergency surgical procedure

Study or Subgroup	Mifepristone + Misoprostol Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Nielsen 1999	0	60	1	62	10 5%	0 34 [0 01 , 8 29]
Torre 2012	4	89	12	85	89 5%	0 32 [0 11 , 0 95]
Total (95% CI)		**149**		**147**	**100.0%**	**0.32 [0.11 , 0.90]**
Total events:	4		13			

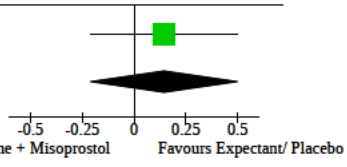
Heterogeneity: Tau² = 0 00; Chi² = 0 00, df = 1 (P = 0 96); I² = 0%
Test for overall effect: Z = 2 16 (P = 0 03)
Test for subgroup differences: Not applicable



Analysis 10.4. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 4: Pain score

Study or Subgroup	Mifepristone + Misoprostol Mean	SD	Total	Expectant/ Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Nielsen 1999	66.1	26.3	60	62	30.1	62	100.0%	0.14 [-0.21 , 0.50]
Total (95% CI)			**60**			**62**	**100.0%**	**0.14 [-0.21 , 0.50]**

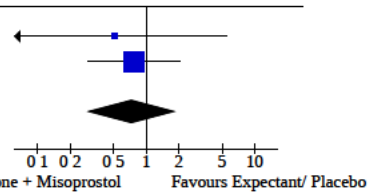
Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 10.5. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 5: Pelvic inflammatory disease, sepsis or endometritis

Study or Subgroup	Mifepristone + Misoprostol Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Nielsen 1999	1	60	2	62	14 4%	0 52 [0 05 , 5 55]
Trinder 2006	7	308	9	306	85 6%	0 77 [0 29 , 2 05]
Total (95% CI)		**368**		**368**	**100.0%**	**0.73 [0.30 , 1.80]**
Total events:	8		11			

Heterogeneity: Tau² = 0 00; Chi² = 0 09, df = 1 (P = 0 76); I² = 0%
Test for overall effect: Z = 0 69 (P = 0 49)
Test for subgroup differences: Not applicable

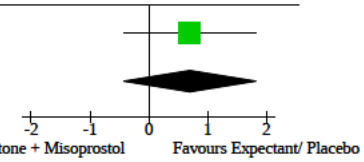


Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 10.6. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 6: Days of bleeding

Study or Subgroup	Mifepristone + Misoprostol Mean	SD	Total	Expectant/ Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nielsen 1999	11	3.26	60	10.3	3.11	62	100.0%	0.70 [-0.43 , 1.83]
Total (95% CI)			**60**			**62**	**100.0%**	**0.70 [-0.43 , 1.83]**

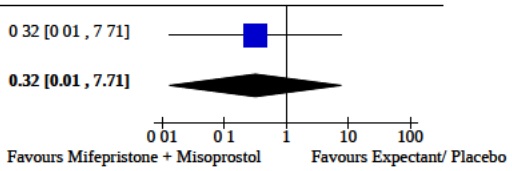
Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 10.7. Comparison 10: Mifepristone + Misoprostol vs Expectant/ Placebo, Outcome 7: Pyrexia

Study or Subgroup	Mifepristone + Misoprostol Events	Total	Expectant/ Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Torre 2012	0	89	1	85	100 0%	0 32 [0 01 , 7 71]
Total (95% CI)		**89**		**85**	**100.0%**	**0.32 [0.01 , 7.71]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0 70 (P = 0 48)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search terms for WHO ICTRP and ClinicalTrials.gov

curettage AND miscarriage

misoprostol AND miscarriage

mifepristone AND miscarriage

vacuum AND miscarriage

expectant AND miscarriage

management AND miscarriage

surgical AND miscarriage

Appendix 2. Global statistical inconsistencies for network meta-analyses

Outcome	P value for global inconsistency
Complete miscarriage	0.000
Complete miscarriage (incomplete miscarriage only)	0.208
Complete miscarriage (missed miscarriage only)	0.105
Composite outcome of death or serious complication	0.570
Need for unplanned/emergency surgical procedure	0.819

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(Continued)

Pain scores (visual analogue scale)	0.696
Re-admission to hospital	0.301
Nausea	-
Vomiting	0.073
Diarrhoea	0.061
Pyrexia	0.208
Change in haemoglobin measurements before and after the miscarriage	0.927
Days of bleeding	0.017
Days of bleeding (incomplete miscarriage only)	0.038
Days of bleeding (missed miscarriage only)	-

HISTORY

Protocol first published: Issue 3, 2017

CONTRIBUTIONS OF AUTHORS

Ioannis D Gallos (IDG) and Arri Coomarasamy (AC) conceived the idea for this review. IDG, AC, Malcolm J Price (MP), Aurelio Tobias (AT), Özge Tunçalp (OT), Antonella Lavelanet (AL) and A Metin Gülmezoglu (AMG) designed the meta-analysis. Jayasish Ghosh (JG) designed the electronic data collection forms. JG, Hannah Jeffery (HJ) and IDG performed study selection. JG, Argyro Papadopoulou (AP), HJ, Adam Devall (AJD), Leanne Beeson (LB) and Vivian Do (VD) performed data extraction. JG performed the pairwise meta-analysis. AT performed the network analysis. JG, AJD, AP and IDG graded the evidence and AP created the "summary of findings table". IDG created the protocol. JG and AJD drafted this review. IDG, AJD and AC edited and revised the review. All authors reviewed the manuscript prior to submission. AJD and IDG are the guarantors for this review.

DECLARATIONS OF INTEREST

Jay Ghosh: Grants and contracts - this work is supported by Tommy's Charity who fund the Tommy's National Centre for Miscarriage Research, which is held by Prof Arri Coomarasamy. Work related to the topic of the review as health professional - O&G Medical Doctor.

Argyro Papadopoulou: I am currently a PhD student at the University of Birmingham, UK. My tuition fees are paid by Tommy's charity.

Adam J Devall: co-investigator for the MifeMiso trial now published in the Lancet, which was funded by the NIHR HTA programme. AJD did not participate in any decisions regarding this trial (i.e. assessment for inclusion/exclusion, trial quality, data extraction) for the purposes of this review or future updates, these tasks have been carried out by other members of the team who were not directly involved in the trial.

Hannah C Jeffery: none known.

Leanne E Beeson: co-investigator for the MifeMiso trial now published in the Lancet, which was funded by the NIHR HTA programme. LEB did not participate in any decisions regarding this trial (i.e. assessment for inclusion/exclusion, trial quality, data extraction) for the purposes of this review or future updates, these tasks have been carried out by other members of the team who were not directly involved in the trial.

Vivian Do: none known.

Malcolm J Price:none known.

Aurelio Tobias: none known.

Özge Tunçalp: none known.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Antonella Lavelanet: I published work as a freelance writer. I am a board certified OBGYN, but I am currently not practicing and have not practiced for the last 4 years.

Ahmet Metin Gülmezoglu: none known.

Arri Coomarasamy: chief-investigator for the MifeMiso trial now published in the Lancet, which was funded by the NIHR HTA programme. AC did not participate in any decisions regarding this trial (i.e. assessment for inclusion/exclusion, trial quality, data extraction) for the purposes of this review or future updates, these tasks have been carried out by other members of the team who were not directly involved in the trial.

Ioannis D Gallos: co-investigator for the MifeMiso trial now published in the Lancet, which was funded by the NIHR HTA programme. IDG did not participate in any decisions regarding this trial (i.e. assessment for inclusion/exclusion, trial quality, data extraction) for the purposes of this review or future updates, these tasks have been carried out by other members of the team who were not directly involved in the trial.

SOURCES OF SUPPORT

Internal sources

- Tommy's National Centre for Miscarriage Research, UK

External sources

- National Institute for Health Research (NIHR), UK

  This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Pregnancy and Childbirth Group

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are some differences between the published protocol for this review (Gallos 2017) and the full review, these are listed below.

Methods/ criteria for considering studies for this review/ types of interventions

The protocol stated the following methods.

We will include the following interventions: dilatation plus sharp curettage, suction curettage, suction curettage with cervical preparation, misoprostol alone, and mifepristone plus misoprostol versus expectant management or placebo.

Instead of dilatation plus sharp curettage we have named this intervention dilatation and curettage. Instead of suction curettage we have named this intervention suction aspiration. Instead of suction curettage with cervical preparation we have named this intervention suction aspiration plus cervical preparation.

We had also planned to include comparisons between different routes of administration of medical treatment (e.g. oral versus vaginal), or between different drugs or doses of drug, or duration or timing of treatment which would have been part of a subgroup analysis. This was not performed as there was significant heterogeneity between the different misoprostol arms present in the trials however this may be examined in a future separate review. We had planned to include a sensitivity analysis to assess different effect measures (risk ratio versus odds ratio), however this was not done because different effect measures cannot be combined in one analysis. We had planned to include a sensitivity analysis to assess use of fixed-effect versus random-effects model, however since fixed effects should only be used in the absence of heterogeneity, this was not done. We have added 'exclusion of quasi-randomised trials' to the planned sensitivity analysis in the methods section. We had also aimed to compare cervical preparation drugs with each other and compare different doses, routes and regimens of the same drug with each other in a subgroup analysis however sufficient data did not exist.

Methods/ data synthesis/ methods for direct treatment comparisons

The protocol stated the following.

We will perform standard pairwise meta-analyses using a random-effects model in the presence of substantial heterogeneity or fixed-effect model in STATA for every treatment comparison.

We performed standard pairwise meta-analyses in Review Manager 5.4 and STATA.

Methods/ subgroup analysis and investigation of heterogeneity

The protocol in this section stated the following.

If we find important heterogeneity or inconsistency, or both, we will explore the possible sources. If sufficient studies are available, we will perform subgroup analyses by using the following effect modifiers:

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

- gestational age (nine weeks versus > nine weeks of gestation);
- type of miscarriage (incomplete versus missed miscarriage);
- type of vacuum aspiration device used (electrical versus manual vacuum aspiration);
- type of healthcare setting (inpatient versus outpatient);
- dosage, regimen, and route of drug administration (sublingual, rectal, oral).

We will assess subgroup differences by evaluating the relative effects and assessment of model fit for the primary outcomes.

Sufficient studies were not available for subgroup analysis of gestational age, type of vacuum aspiration device used and dosage, regimen, and route of drug administration (sublingual, rectal, oral). The detail in the study characteristics of included studies was not sufficient enough, in order to perform the subgroup analysis of type of healthcare setting.

Methods/ sensitivity analysis

The protocol in this section stated the following.

For the primary outcomes we will perform sensitivity analysis for the following:

- overall risk of bias of the studies (low versus high risk of overall bias);
- randomisation unit (cluster versus individual);
- different effect measures (risk ratio versus odds ratio);
- use of fixed-effect versus random-effects model;
- use of placebo versus expectant management

We will assess differences by evaluating the relative effects and assessment of model fit.

There were no cluster-randomised trials included to allow us to perform a sensitivity analysis based on randomisation unit. Other planned sensitivity analyses were performed but no differences were detected in terms of the overall results.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Incomplete [therapy]; Abortion, Missed [therapy]; Abortion, Spontaneous [*therapy]; Drug Therapy, Combination; Mifepristone [administration & dosage]; Misoprostol [administration & dosage]; Network Meta-Analysis; Oxytocics [administration & dosage]; Placebos [administration & dosage]; *Pregnancy Trimester, First; Randomized Controlled Trials as Topic; Suction [statistics & numerical data]; Vacuum Curettage [statistics & numerical data]; Watchful Waiting [statistics & numerical data]

MeSH check words

Female; Humans; Pregnancy

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Page 126: End of publication

The manuscript that preceeds this page has been published by *Cochrane.*

Publication 2: Ghosh J, Papadopoulou A, Devall AJ, Jeffery HC, Beeson LE, Do V, Price MJ, Tobias A, Tunçalp Ö, Lavelanet A, Gülmezoglu AM, Coomarasamy A, Gallos ID. **Methods for managing miscarriage: a network meta-analysis**. Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD012602. DOI: 10.1002/14651858.CD012602.pub2.

CHAPTER FIVE:

PREVENTION AND MANAGEMENT OF MISCARRIAGE: A NARRATIVE SYSTEMATIC OVERVIEW REVIEW OF REVIEWS

Authors and contributions:

Dr Jayasish Ghosh conceived the concept, created the search strategy, carried out the search, acted as the first reviewer for study selection, data extraction, quality assessment, created the tables, and wrote the manuscript.

Dr Rima Dhillon-Smith acted as the second reviewer for study selection, data extraction and quality assessment, and co-created the tables.

Mr Derek Yates advised on the literature search strategy.

Dr Ioannis D Gallos provided comments on the manuscript.

Prof Arri Coomarasamy co-conceived the idea, acted as the final decision maker over author disagreements, and provided comments on the manuscript.

Abstract

Research question

What is the current body of evidence on the management of miscarriage and recurrent miscarriage?

Design

A narrative systematic overview of systematic reviews of randomised trials where miscarriage or live-birth was reported as an outcome.

Results

There are several systematic reviews of randomised trials, which encompass a broad range of behavioural, medical, surgical, and complementary interventions which examine their impact on miscarriage. The majority of the evidence is of low or moderate certainty.

Conclusion

Women and couples should be adequately counselled regarding the lack of high-quality evidence for many interventions, for the management of miscarriage and recurrent miscarriage. Further high-quality randomised trial-level evidence is required for many interventions to inform and improve the quality of recommendations for the management of miscarriage and recurrent miscarriage.

Introduction

Miscarriage is a very common early pregnancy problem and it has significant societal level costs, from the economic costs of lost productivity, to the healthcare-related costs associated with its' treatment. Estimates have put the cost of the management of miscarriage and its' related complications for the NHS at approximately £350,000,000 per annum (165,166). The true economic costs of miscarriage in its entirety, are currently unknown but are likely to be substantial, and there is research currently being conducted to establish the size of this cost (167). There are individual-level costs, both physical-health morbidity and mortality, and also the mental-health burden of this common early pregnancy complication (15). These costs are borne not only by the women that suffer the miscarriages but also their partners who also suffer a loss (16).

In this thesis so far, we have introduced the female reproductive anatomy, introduced miscarriage and recurrent miscarriage and their definitions and meanings. We have also discussed the many known risk factors and causes of miscarriage, as well as how it is currently managed. We explored the role of the fallopian tubes in the process of conception and how fallopian tube disease may impact upon this process. We then discussed the work that I have undertaken to further this knowledge. We discussed in chapter two, new systematic review evidence that suggests that fallopian tube disease in the form of hydrosalpinx may increase the risk of miscarriage and, in particular, when the pregnancy is in the biochemical phase. We discussed how surgical treatment may reduce the risk of further miscarriage. In chapter three, we then discussed primary-data that suggests hydrosalpinx appears to be less common in the

recurrent miscarriage population compared to the subfertile population. And primary observational data which corroborates the previous systematic review evidence in chapter two, that these women with tubal pathology have worse pregnancy outcomes. And finally, in chapter four, we explored new network meta-analysis evidence on how miscarriage may best be managed once it has occurred.

The work I have performed is but a fraction of what is needed to improve the care of women who suffer from a miscarriage. In this chapter, we will explore the evidence that already exists regarding miscarriage. This includes how miscarriage maybe reduced and how miscarriage is currently managed. We wanted to synthesise all systematic reviews of randomised trials of any intervention where miscarriage was an outcome to explore how we can reduce miscarriage. And also, to highlight where future research should be directed due to a paucity of evidence entirely or a lack of good quality or high certainty evidence.

To conclude this body of work, we set out to narratively synthesise all the systematic review evidence of randomised trials that exists in the medical literature regarding miscarriage. We aimed to include any clinical, behavioural or health-system intervention.

Methods

Literature search

We searched two resources to find all systematic reviews that reported our outcomes of interest. Using the Pubmed systematic review filter text, we searched Pubmed clinical queries (inception till 9 January 2020). With assistance from an information scientist, we used the following key-words for our search on Pubmed: miscarriage OR pregnancy loss OR spontaneous abortion OR foetal demise OR fetal demise OR intrauterine demise OR foetal death OR fetal death OR intrauterine death OR foetal loss OR fetal loss OR intrauterine loss. We also searched the Cochrane database of systematic reviews (CDSR) (inception till 9 January 2020). Finally, we hand-searched the reference lists of systematic reviews we had already included, for any reviews with relevant outcomes, which met our eligibility criteria that were missed from the previously conducted literature searches and study selection process.

Inclusion and exclusion criteria

We included any systematic review and meta-analysis of randomised trials which reported the outcome of miscarriage or live-birth. Or any systematic review and meta-analysis, where the meta-analysis only for randomised trial data, was able to be extracted for the outcome of miscarriage or live birth. We also included systematic reviews and network meta-analyses (NMA). Many reviews looked at interventions in the infertile population undergoing assisted reproductive treatment (ART). If the review population was exclusive to women undergoing ART and the intervention could not apply to women with natural conceptions, then it was excluded. If the population was exclusively women undergoing ART but the intervention could be used for women with, for example recurrent miscarriage or women with natural conceptions then that review was included. This overview review was not limited to

treatments solely available in the UK. We used the eligibility, inclusion and exclusion criteria outlined in Table 14 for study selection.

Table 14: Table of inclusion and exclusion criteria for review selection

Eligibility		**Inclusion**	**Exclusion**
Participant level	**Population**	Pregnant women with a singleton pregnancy Women trying to become pregnant	Studies that exclusively reported on subfertile women
Review level	**Review**	Systematic reviews	Overview reviews
	Trial design	Randomised clinical trials (including cluster- or quasi-randomised trials) Any setting or year	Non-randomised study designs
	Intervention	Any behavioural, clinical or health-systems intervention	Interventions exclusive to subfertile women
	Comparison	Alternative intervention or no intervention (including placebo)	
	Outcome	Miscarriage outcome (any)	Miscarriage outcome not specified or reported

Study selection

Two reviewers independently screened all the titles and abstracts retrieved from literature searches and removed all papers which did not meet our pre-specified inclusion and exclusion criteria (Table 14). The same two reviewers then examined the full texts of the remaining

reviews to remove reviews that had been superseded by more up to date or comprehensive reviews or were duplicates. A further round of study selection was conducted by the same two reviewers, who removed all reviews which could only be exclusively applied to the subfertile population. Disagreements during this process were resolved though discussion with a third reviewer.

Data extraction

Two reviewers independently extracted the required data from included reviews. Any disagreements were resolved with discussion or if required by a third reviewer. The information detailed in Table 15 was extracted from every review that was included.

Table 15: Table of information extracted from each included review

1	*Review title, author and year of publication*
2	*Number of trials contributing data to meta-analyses included in the review*
3	*Number of participants contributing to meta-analyses included in the review*
4	*Quality assessment of comparisons presented or risk of bias assessment of contributory trials*
5	*Overview outcomes of miscarriage and live birth with meta-analyses*
6	Implications for practice or research

Assessment of methodological quality of reviews

We used the GRADE methodology for the assessment of the quality of the evidence that the reviews presented (168). Where GRADE assessment was performed by the included review, we reported this. Where this was not reported, we performed GRADE assessment using the

methods outlined in the GRADE Handbook (169). We used information provided by the paper and if needed the supplementary information. We used information from the table of characteristics and the risk of bias assessment provided by the reviews to assess for the domains of study design, design limitations, and indirectness. We used the provided forest plots to assess for imprecision. Where funnel plots were provided, we were able to assess for publication bias. Where information such as the risk of bias or quality assessment of the contributory papers to the review was not completely provided, we were unable to perform a GRADE assessment. In these instances, the two reviewers made a subjective assessment of quality or risk of bias based on what information was provided by the paper. Any disagreements were resolved through discussion or involvement of a third reviewer. When forming overall assessments of risk of bias, we used the domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We did not mark trials as high risk of bias if they were unable to be blinded due to the nature of their interventions and gave more importance to random sequence generation and allocation concealment.

Data Presentation

We categorised the included papers into three areas:

1. Prevention of miscarriage in asymptomatic women
2. Prevention of miscarriage in symptomatic women
3. Management of miscarriage

We further subcategorised the papers in each of the three categories above, into rational groups as agreed upon by the first and second reviewer. The data is presented in the results section according to these categories. The data that is presented is primarily from natural conceptions. If the data from a review also included subfertile women, we presented the data from natural conceptions, if this was able to extracted separately. If this was not possible, as the data was combined, then we still presented this. Where the data was exclusively from subfertile women, we did not present this information.

For meta-analyses, we presented the summary statistics as provided by the paper, for example risk ratio (RR), odds ratio (OR) or peto odds ratio (POR). It should be noted that RR in the results section referred to risk ratio. If the paper instead presented relative risk, this was stipulated at the beginning of the results for that review. If the paper did not provide these statistics, we presented the crude miscarriage or live-birth rates. For network meta-analyses, we presented the Surface Under the Cumulative RAnking curve (SUCRA). If the NMA did not present the SUCRA, then we presented the summary statistics that were presented using the same method we used for meta-analyses. We did not present comparisons where there was no data available for our outcomes of interest.

Outcomes presented

Our primary focus was miscarriage and so this outcome was presented. We also presented the outcome of live-birth where this was reported, as it is an important and clinically relevant

outcome related to miscarriage. We accepted the definitions for outcomes used by the papers' themselves.

Results

Study selection

We received 1743 results using our search strategy. Using the criteria outlined in Table 14, our first round of study selection based on screening titles and abstracts, removed 1453 results. This left 290 results, of which a further 73 were excluded on the basis they were duplicates or had been superseded by more recent reviews and 109 were excluded as they could only have been applied exclusively to the subfertile population. The full-text of the remaining 108 results were examined and a further 56 were excluded for the reasons given. The reasons for exclusion based on examination of the full-texts of reviews for the final round of study selection are summarised in Table 16. The study flowchart summarising the study selection process is presented in Figure 17.

Table 16: Summary of reasons for exclusion of studies during full-text review

Reasons for removal after full text review	
Data overlapping with newer paper	22
Overview of reviews	3
Miscarriage and live birth data combined and unable to extract	7
No miscarriage or live birth data reported	12
Proposed review withdrawn	2
No RCT data	3
Unable to separate RCT and cohort data	2
Termination/ abortion not miscarriage	2
Commentary only	1
PGS reviews with no RCT data	3
	n=56

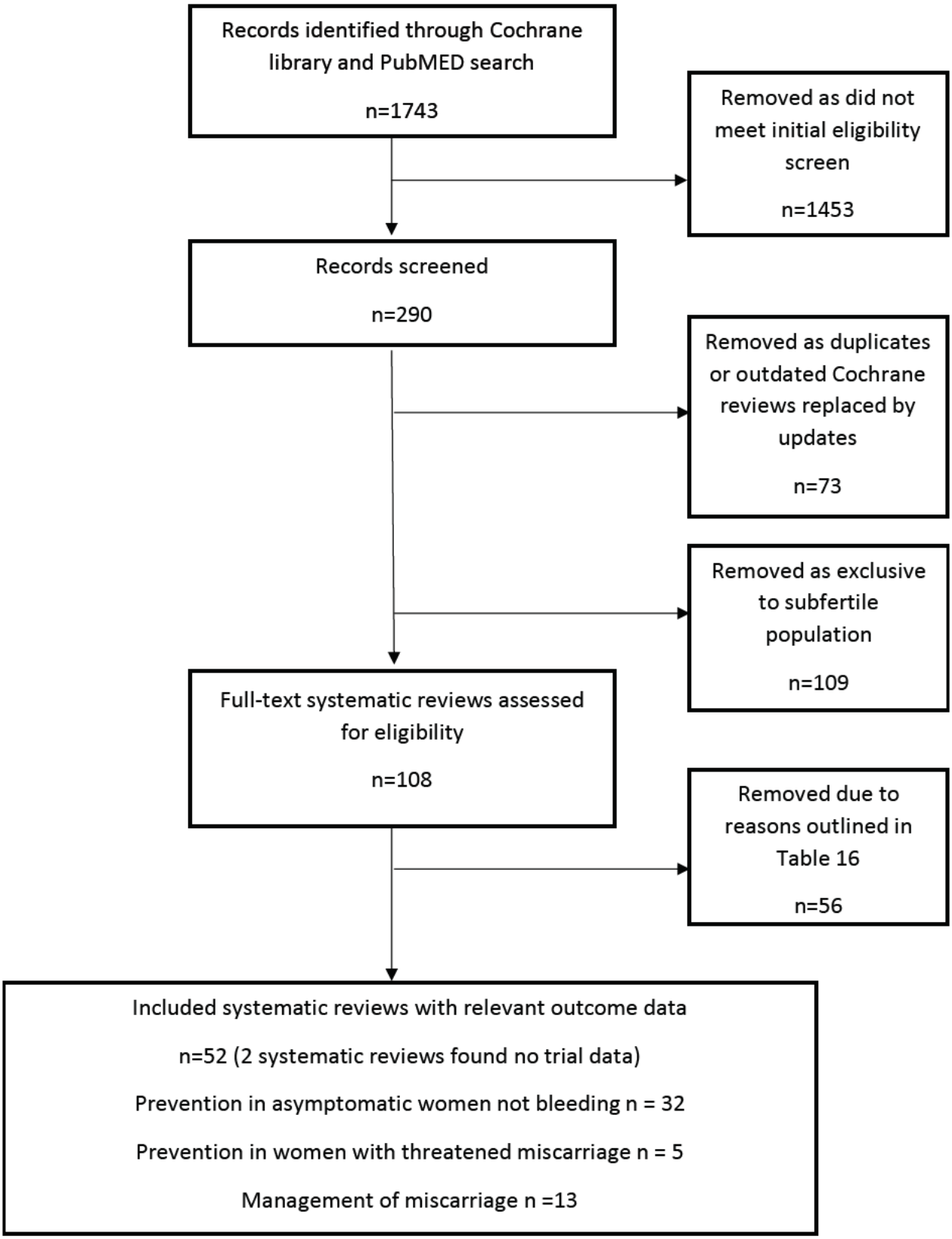


Figure 17: Flowchart of study selection process

Prevention of miscarriage in asymptomatic women

Thirty-two reviews examined interventions to reduce miscarriage in asymptomatic women both in the pre-pregnancy period and during pregnancy. The full results from all included reviews are presented in Table 17.

Immunotherapy interventions

There were three reviews (Achilli 2018, Wong 2014, Dan 2015) that examined immunotherapy interventions to reduce miscarriage (170–172). All three had similar populations looking at the unexplained recurrent miscarriage population. There was some overlap of interventions examined, with intravenous immunoglobulin (IVIG) and prednisolone appearing in two reviews. Achilli 2018 looked at multiple interventions. They found no difference with the use of pre-ovulatory IVIG for miscarriage (OR 0.50; 95% CI 0.18, 1.38) or live-birth (OR 1.56; 95% CI 0.79, 3.09). Similarly, no difference was found for post-pregnancy IVIG for miscarriage (OR 1.01; 95% CI 0.42, 2.39) or live-birth (OR 0.98; 95% CI 0.39, 2.17). Wong 2014 also found no difference with the use of IVIG for live-birth (POR 0.98;95% CI 0.61, 1.58). Achilli 2018 found Lymphocyte immunotherapy had no benefit for either miscarriage (OR 0.48; 95% CI 0.01, 25.44) or for live-birth (OR 1.96; 95% CI 0.32, 12.13). Meta-analysis was not possible for Granulocyte colony stimulating factor (G-CSF) versus control and so crude miscarriage rates (17.2% vs. 51.5%, *p*=0.0061) and live-birth rates (82.8% vs. 48.5%, *p*=0.0061) were presented, but this was data from one small trial. Achilli 2018 presented crude rates for oral prednisolone versus control for miscarriage (40% vs. 60%, *p*=not significant) and live birth (60% vs. 40%, *p*=not significant). Dan 2015 performed meta-analysis from two small trials and found

prednisolone may improve pregnancy outcomes for both miscarriage (RR 0.50; 95% CI 0.31, 0.81) and live-birth (RR 1.58; 95% CI 1.23, 2.02) when compared to placebo. Wong 2014 also looked at paternal white cell immunisation (POR 1.23; 95% CI 0.89, 1.70), donor white cell immunisation (POR 1.39; 95% CI 0.68, 2.82) and trophoblast membrane immunisation (POR 0.40; 95% CI 0.11, 1.45) compared to placebo and found no significant benefit. Overall, there were minimal clinically significant results and, where it was able to be GRADE assessed, no high-quality evidence for the use of any immunotherapy to reduce miscarriage. This is reflected in the recommendations by the authors of the reviews.

It should be noted that concerns previously existed over the use of systemic corticosteroids in early pregnancy on the unborn fetus. Initial concerns existed over an increase in the risk of oral and facial clefts and subsequent concerns arose over fetal growth restriction as well as pre-term birth, preeclampsia and gestational diabetes mellitus (173). The most recent systematic review level evidence found that recent evidence did replicate previous concerns over clefts and no studies since 2003 have shown a statistically significant increase in risk (173). It was also noted by Bandoli 2018 that most of the evidence did not control for the increase in risk from the underlying maternal health condition that necessitated the administration of the systemic corticosteroid. Bandoli 2018 also found there was little evidence for an independent increase in the risks of preterm birth, growth restriction or preeclampsia and no sufficient evidence to ascertain if corticosteroids increase the risk of gestational diabetes mellitus.

Anti-coagulants and anti-platelet interventions

Four reviews (Areia 2015, De Jong 2014, Liu 2020, Zhang 2015) examined anticoagulants and antiplatelet interventions to reduce miscarriage (174–177). The populations they examined varied with Areia 2015 looking at women with hereditary thrombophilia such as factor V Leiden (FVL), methylenetetrahydrofolate reductase (MTHFR), prothrombinG20210A (PTm) mutations and protein C, protein S, and antithrombin 3 deficiencies. Whereas, De Jong 2014 looked at women with two or more unexplained miscarriage with and without concurrent inherited thrombophilia. Similarly, Zhang 2015 looked at women with two or more unexplained miscarriages with or without a thrombophilia and women with APS and two or more otherwise unexplained miscarriages. Liu 2020 examined women with APS and two or more consecutive pregnancy losses. The interventions examined across all four reviews were combinations of aspirin, low molecular weight heparin (LMWH), and unfractionated heparin (UFH). Areia 2015 found very-low-quality evidence that there was no benefit of adding LMWH to aspirin compared to aspirin alone for miscarriage (OR 0.69; 95% CI 0.22, 2.16), or live birth (OR 1.70; 95% CI 0.72, 4.0) for women with a hereditary thrombophilia. De Jong 2014 found no benefit for the use of aspirin (RR 0.94; 95% CI 0.80, 1.11) or LMWH (RR 1.23; 95% CI 0.84, 1.81) or combined aspirin and LMHW (RR 1.01; 95% CI 0.87, 1.16) compared to no treatment for live-birth. LMWH and aspirin were also compared to each other (RR 1.16; 95% CI 0.93, 1.45) and no difference was found for live-birth. Further comparisons using various combinations of the two interventions were conducted, and similarly, no differences were found. Liu 2020 and Zhang 2015 were both network meta-analyses (NMA). Zhang 2015 ranked interventions and found that for women with two or more miscarriages and APS, UFH plus

aspirin (SUCRA=75.5%) ranked first, LMWH (SUCRA=71%) second, placebo third (SUCRA=47.7%), LMWH plus aspirin fourth (SUCRA=34.4%) and aspirin fifth (SUCRA=23%) for live-birth. This suggests aspirin may have a negative effect on pregnancy outcomes in this cohort of women. Liu 2020 did not present SUCRAs so was not able to rank interventions in order of effectiveness for outcomes. Liu 2020 found no difference for live-birth, for placebo versus aspirin (OR 2.31; 95% CI 0.47, 6.63), versus LMWH (OR 1.50; 95% CI 0.09, 5.32), or versus aspirin plus LMWH (OR 0.77; 95% CI 0.17, 2.22). Overall, there was a lack of high-quality evidence for the use of anticoagulants, antiplatelets or a combination of anticoagulants and antiplatelets in unexplained recurrent miscarriage with or without thrombophilia, and the review authors highlighted a need for further high-quality research.

Hormonal and endocrine interventions

Eight reviews looked at endocrinological interventions; three looked at sex steroids (Carp 2015, Haas 2019, Lim 2013) (178–180), three looked at the thyroid (Earl 2013, Rao 2019, Reid 2013) (181–183), and one each looked at dopamine agonists (Chen 2016) (184) and human chorionic gonadotrophin (hCG) (Morley 2013) (185). Carp 2015 looked at the use of oral dydrogesterone in women with three or more miscarriages and found moderate-quality evidence of a benefit in reducing miscarriage compared to a control (OR 0.35; 95% CI 0.19, 0.65). Haas 2019 also found moderate-quality evidence that progesterone may be beneficial for miscarriage risk (RR 0.73: 95% CI 0.54, 1.00) and live-birth (RR 1.07; 95% CI 1.00, 1.13), compared to placebo or no treatment, in women with recurrent miscarriage of unclear aetiology. Lim 2013 found that in women with a long history of diabetes, there was low-quality

evidence that there was no benefit for oestrogen plus progesterone compared to placebo (RR 0.95; 95% CI 0.32, 2.80) for miscarriage. And very-low-quality evidence that in pregnant women who had undergone IVF, there was no benefit for oestrogen plus progesterone compared to no treatment (RR 0.66; 95% CI 0.23, 1.85) for miscarriage.

Earl 2013 looked at women with hyperthyroidism during pregnancy but did not find any trials which compared antithyroid interventions to a control. Rao 2019 looked at women with subclinical hypothyroidism and found moderate-quality evidence of benefit for the use of levothyroxine compared to no treatment or placebo (RR 0.27; 95% CI 0.14, 0.52) for miscarriage. For women with thyroid autoimmunity, Rao 2019 found high-quality evidence of benefit for levothyroxine over no treatment or placebo (RR 0.68; 95% CI 0.48, 0.97) for miscarriage. Reid 2013 looked at women with hypothyroidism or subclinical hypothyroidism during pregnancy and found no benefit for selenomethionine compared to placebo for miscarriage (RR 0.85; 95% CI 0.30, 2.42), but it was very-low-quality evidence from one small RCT.

Chen 2016 found low-quality evidence of the benefit of oral bromocriptine compared to no treatment for miscarriage (RR 0.28; 95% CI 0.09, 0.87), but very-low-quality evidence of no benefit for live-birth (RR 1.50; 95% CI 0.93, 2.42) both from one small RCT in women with recurrent miscarriage and idiopathic hyperprolactinaemia.

Morley 2013 found low-quality evidence, that in women with unexplained recurrent miscarriage (≥ three consecutive pregnancy losses), there was no benefit of hCG for miscarriage compared to no treatment or placebo in high-quality trials (RR 0.74; 95% CI 0.44, 1.23).

Overall, there appears to be some possible benefit for the use of progesterone in women with unexplained recurrent miscarriage and benefit for levothyroxine in women with hypothyroidism. There is no evidence for the use of bromocriptine in women with idiopathic hyperprolactinaemia and recurrent miscarriage or for the use of hCG in women with unexplained recurrent miscarriage. Further high-quality research is needed before firm conclusions can be reached with these groups, as well as for the use of antithyroid medications in women with hyperthyroidism as at the current time, no evidence exists.

Insulin sensitising interventions

There were two reviews (Morley 2017, Palomba 2009) which looked at insulin-sensitising agents in women with polycystic ovarian syndrome (PCOS) (186,187). Palomba 2009 found no evidence for the benefit of metformin started pre-conceptually for miscarriage (OR 0.89; 95% CI 0.65, 1.21). Morley 2017 found low-quality evidence of possible benefit for live-birth (OR 1.59; 95% CI 1.00, 2.51) but no evidence of benefit for miscarriage (OR 1.08; 95% CI 0.50, 2.35) in women with PCOS and subfertility. Specifically, for women with PCOS alone, Morley 2017 found very-low-quality evidence of no benefit of metformin compared to clomiphene for miscarriage (OR 0.92; 95% CI 0.50, 1.67) or live-birth (OR 1.71; 95% CI 1.00, 2.94). Morley 2017

also found low-quality evidence of some benefit for metformin plus clomiphene versus clomiphene for miscarriage (OR 1.59; 95% CI 1.03, 2.46), but not for live-birth (OR 1.21; 95% CI 0.92, 1.59). Overall, the authors felt there may be some benefit of metformin over placebo for pregnancy outcomes in women with PCOS but further high-quality research is required, especially for metformin started preconceptually and continued throughout the first trimester. This is also the case for different subgroups of women with PCOS for example, stratified by BMI.

Cervical cerclage interventions

Alfirevic 2017 was the only included review looking at cervical cerclage interventions (188). They looked at women with a singleton pregnancy deemed at high-risk of a miscarriage either due to ultrasound evidence of a shortened cervix, their obstetric history or based on clinical examination. For this group, for the outcome of miscarriage, they found moderate-quality evidence of no benefit of cerclage over no cerclage (RR 0.84; 95% CI 0.58, 1.22), no benefit of cerclage compared to vaginal progesterone (RR 0.58; 95% CI 0.17, 2.01) and no benefit of cerclage compared to intramuscular progesterone (RR 1.47; 95% CI 0.38, 5.73). They also found moderate-quality evidence of no difference between history-indicated versus ultrasound-indicated cerclage for miscarriage. Therefore, they concluded that the benefits of cerclage with regard to miscarriage and live-birth remain unanswered.

Surgical interventions

Rikken 2017 was the only included review that looked at surgical interventions (189). They examined women of reproductive age with a septate uterus and would have compared hysteroscopic resection compared to no treatment. Unfortunately, they did not find any published trials which made this comparison. Therefore, high-quality research is needed in this area.

Endometrial injury interventions

Lensen 2016 was the only included review that looked at endometrial injury (190). They looked at subfertile women attempting to conceive with sexual intercourse (SI) or intrauterine insemination (IUI). For miscarriage, they found very-low-quality evidence of no benefit for endometrial injury versus no treatment or a sham procedure (RR 0.73; 95% CI 0.38, 1.39). However, looking specifically at women attempting to conceive with SI, they found very-low-quality evidence of some benefit for live-birth (RR 2.48; 95% CI 1.12, 5.49). Their overall conclusion was that there was insufficient evidence to state that endometrial injury has a benefit for pregnancy outcomes.

Lifestyle interventions

There were two reviews (Aleman 2005, Furber 2013) that looked at lifestyle interventions (191,192). Furber 2013 looked at obese pregnant women and would have compared weight-loss interventions to routine care, however, no RCTs were identified by the authors. Aleman 2005 looked at bed-rest in women at high-risk of miscarriage. They found very-low-quality

evidence that for miscarriage, there was no benefit of bed-rest over no bed-rest (RR 1.54; 95% CI 0.92, 2.58), no benefit of bed-rest in a hospital over no bed-rest (RR 0.42; 95% CI 0.02, 8.91) and no benefit of bed-rest at home over no bed-rest (RR 1.66; 95% CI 0.99, 2.77). However, they did find that bed-rest was worse than hCG for reducing miscarriage (RR 2.5; 95% CI 1.22, 5.11). Overall, the meta-analyses were based on one or two RCTs and all the evidence was of very-low-quality. For these reasons, the authors concluded there was insufficient evidence to support a policy of bedrest in order to prevent miscarriage.

Micronutrient interventions

There were three reviews (Balogun 2016, De-Regil 2015, Keats 2019) looking at various micronutrient interventions (193–195). De-Regil 2015 looked at folate in women under 12 weeks of gestation and found moderate-quality evidence of no benefit of folate compared to no intervention or placebo or a micronutrient that does not contain folate (RR 1.10; 95% CI 0.94, 1.28) for reducing miscarriage. Keats 2019 also looked at the same population and found high-quality evidence of no benefit of multiple micronutrients plus iron plus folate compared to iron with or without folate for reducing miscarriage (RR 0.99; 95% CI 0.94, 1.04). Balogun 2016 looked at more comparisons. They found that for early or late miscarriage, there was moderate-quality evidence of no benefit of vitamin C plus vitamin E over a control (RR 0.90; 95% CI 0.65 to 1.26), low-quality evidence of no benefit of vitamin A plus iron plus folate versus iron plus folate (RR 0.86; 95% CI 0.46, 1.62) and moderate-quality evidence of no benefit of multivitamins plus iron plus folate versus iron plus folate (RR 0.98; 95% CI 0.94, 1.03). There were six further comparisons, none of which provided evidence of a benefit of a micronutrient

over another or compared to no micronutrient. And so, the authors concluded that no micronutrients, taken before or during pregnancy, prevent women from experiencing a miscarriage and that there is insufficient evidence in terms of different combinations of micronutrients on the outcome of miscarriage. This lack of evidence of benefit was echoed by the authors of the other two reviews by De-Regil 2015 and Keats 2019.

Complementary interventions

Two reviews (Li 2016, Yang 2013) looked at complementary interventions and both examined Chinese herbal medicines (CHM) in women with recurrent miscarriage (196,197). Li 2016 found very-low-quality evidence that there was no benefit of CHM versus other pharmaceuticals (RR 1.05; 95% CI 0.67, 1.65) for live-birth. However, Li 2016 also found evidence of benefit for CHM plus other pharmaceuticals versus other pharmaceuticals alone (RR 1.55; 95% CI 1.14, 2.10), and for CHM plus psychotherapy compared to psychotherapy alone (RR 1.32; 95% CI 1.07, 1.64) for live-birth. However, both of these comparisons were of very-low-quality evidence and hence authors suggested there was limited evidence for the use of CHM for treating unexplained recurrent miscarriage, and that further high-quality evidence is needed particularly to evaluate safety. Yang 2013 also looked only at live-birth. They found evidence of benefit for CHM versus progesterone (RR 1.31; 95% CI 1.13, 1.52), of benefit for CHM versus progesterone plus hCG (RR 1.25; 95% CI 1.06, 1.47), of benefit for CHM plus conventional medicine versus progesterone (RR 1.17; 95% CI 1.07, 1.29) and of benefit for CHM plus conventional medicine versus hCG (RR 1.20; 95% CI 1.01, 1.43). Yang 2013 found no benefit of CHM plus conventional medicine versus progesterone plus hCG (RR 1.08; 95% CI

0.93, 1.25). However, the quality of the evidence was not high for any of the comparisons, it was moderate for CHM versus progesterone and low or very-low for the other comparisons. The authors suggested that some CHM, particularly in combination with progesterone, may have some beneficial effect on improving live-birth, however, further evidence is required particularly to evaluate safety.

Other interventions

There were five remaining reviews that we felt could not be classified in the same manner as the other reviews. Boelig 2016 primarily looked at interventions for treating hyperemesis gravidarum but included miscarriage as an outcome for four comparisons (198). They found no evidence for harm or benefit with regard to miscarriage for acupuncture and acupressure versus placebo (RR 0.48; 95% CI 0.05, 5.03), midwife-led outpatient care versus routine care (RR 0.96; 95% CI 0.15, 6.34), corticosteroids versus placebo (RR 0.64; 95% CI 0.11, 3.70), or adrenocorticotrophic hormone (ACTH) versus placebo (RR 1.00; 95% CI 0.07, 14.64). All this evidence was either low or very-low quality evidence from single small RCTs.

Brocklehurst 2013 looked at pregnant women with bacterial vaginosis (BV) or intermediate vaginal flora, irrespective of whether it has been detected through antenatal screening or because a woman was symptomatic (199). They found moderate-quality evidence from single RCTs, that oral clindamycin compared to placebo reduced the risk of late miscarriage (RR 0.20; 95% CI 0.04, 0.89), however, low-quality evidence suggested vaginal clindamycin compared to no treatment does not appear to have the same benefit (RR 0.20; 95% CI 0.01, 4.10).

Brown 2015 found very-low quality evidence from a single RCT, that there was no reduction in miscarriage from pregnant women carrying their own case notes compared to women carrying a “co-op” card with the full notes being retained by the hospital (RR 1.19; 95% CI 0.45, 3.16) (200).

Claire 2020 found low-quality evidence from five RCTs that nicotine replacement therapy (NRT) had neither a positive nor negative impact compared to a control (RR 1.60; 95% CI 0.53, 4.83) for miscarriage (201).

González 2018 looked at the miscarriage risk with women receiving mefloquine for malaria prevention (202). They found no evidence of an increased or decreased risk of miscarriage with mefloquine versus cotrimoxazole (RR 1.07; 95% CI 0.07, 16.84), or with mefloquine versus placebo (RR 0.48; 95% CI 0.04, 5.22). However, the evidence was of a very-low-quality from single RCTs.

Article, author, year of publication and journal	Number of trials with data for miscarriage or live birth	Total number of partici-pants in the meta-analysis	Summary findings for outcomes of miscarriage and live birth and assessment for quality of evidence	Implications for practice or research
Immunotherapy interventions			vs: versus, OR: Odds ratio, RR: Risk ratio, CI: Confidence interval, NS: Not significant, RCT: Randomised controlled trial, n: Number of participants in that comparison	
The role of immunotherapy in in vitro fertilization and recurrent pregnancy loss Achilli 2018 Fertility and Sterility	15	946	**Population: Primary idiopathic recurrent pregnancy loss (RPL)** <u>Outcome: Miscarriage</u> 1) Intravenous Immunoglobulin (pre-ovulatory) vs control OR = 0.50 (95% CI 0.18 to 1.38), 2 RCTs, n=98 LOW quality evidence 2) Intravenous Immunoglobulin (post-pregnancy) vs control OR 1.01 (95% CI 0.42 to 2.39), 3 RCTs, n=120 LOW quality evidence 3) Lymphocyte immunotherapy vs control OR 0.48 (95% CI 0.01 to 25.44). 2 RCTs, n=63 LOW quality evidence 4) Oral prednisolone vs control Crude miscarriage rates: 40% vs. 60%, *p*=NS, 1 RCT, n=40.	Insufficient evidence to recommend routine use of immunotherapy for improving pregnancy outcomes. Further high-quality evidence is needed.

			LOW risk of bias (unable to GRADE assess) 5) Granulocyte colony stimulating factor vs control Crude miscarriage rates: 17.2% vs. 51.5%, *p*=0.0061, 1 RCT, n=68 LOW risk of bias (unable to GRADE assess) <u>Outcome: Live birth</u> 1) Intravenous Immunoglobulin (pre-ovulatory) vs control OR 1.56 (95% CI 0.79 to 3.09), 2 RCTs, n=157 LOW quality evidence 2) Intravenous Immunoglobulin (post-pregnancy) vs control OR 0.98 (95% CI 0.39 to 2.17), 3 RCTs, n=123 LOW quality evidence 3) Lymphocyte immunotherapy vs control OR 1.96 (95% CI 0.32 to 12.13), 3 RCTs, n=137 LOW quality evidence 4) Oral prednisolone vs control Crude Live birth rates: 60% vs. 40%, *p*=NS, 1 RCT, n=40 LOW risk of bias (unable to GRADE assess) 5) Granulocyte colony stimulating factor vs control Crude Live birth rates: 82.8% vs. 48.5%, *p*=.0061, 1 RCT, n=68 LOW risk of bias (unable to GRADE assess)	

			Population: Secondary idiopathic recurrent pregnancy loss (RPL) <u>Outcome: Miscarriage</u> 1) Intravenous Immunoglobulin (pre-ovulatory) vs control Crude miscarriage rates: 5.88% vs. 6.25%, *p*=NS, 1 RCT, n=47 LOW risk of bias (unable to GRADE assess) 2) Intravenous Immunoglobulin (post-pregnancy) vs control OR 1.13 (95% CI 0.46 to 2.77), 2 RCTs, n=103 LOW quality evidence <u>Outcome: Live birth</u> 1) Intravenous Immunoglobulin (pre-ovulatory) vs control Crude Live birth rates: 70% vs. 63%, *p*=0.76, 1 RCT, n=47 LOW risk of bias (unable to GRADE assess) 2) Intravenous Immunoglobulin (post-pregnancy) vs control OR 1.45 (95% CI 0.73 to 2.90), 3 RCTs, n=137 LOW quality evidence	
Immunotherapy for recurrent miscarriage Wong 2014	20	1137	**Population: Women with 3 or more miscarriages and normal evaluations for parental karyotype, antiphospholipid syndrome, uterine anatomy, luteal phase defect.** <u>Outcome: Live birth</u>	Paternal cell immunisation, third-party donor leukocytes,

Cochrane			1) Paternal white cell immunization vs placebo Peto OR 1.23 (95% CI 0.89 to 1.70), 12 RCTs, n=641 MODERATE quality evidence 2) Donor white cell immunization vs placebo Peto OR 1.39 (95% CI 0.68 to 2.82), 3 RCTs, n=156 LOW quality evidence 3) Trophoblast membrane immunization vs placebo Peto OR 0.40 (95% CI 0.11 to 1.45). 1 RCT, n=37 LOW quality evidence 4) Intravenous immunoglobulin vs placebo Peto OR 0.98 (95% CI 0.61, 1.58). 8 RCTs, n=303 MODERATE quality evidence	trophoblast membranes, and intravenous immunoglobulin provide no significant beneficial effect over placebo in improving the live birth rate or lowering the risk of future miscarriage in women who have recurrent miscarriages.
Effect of Prednisolone Administration on Patients with Unexplained Recurrent Miscarriage and in Routine Intracytoplasmic Sperm Injection: A Meta-Analysis Dan 2015	3	326	**Population: Idiopathic recurrent pregnancy loss (RPL)** <u>Outcome: Miscarriage</u> 1) Prednisolone vs Placebo RR 0.50 (95% CI 0.31 to 0.81), 2 RCTs, n=176 2) Prednisolone vs Low dose aspirin + Heparin RR 0.33 (95% CI 0.23 to 0.47), 1 RCT, n=150 <u>Outcome: Live birth</u> 1) Prednisolone vs Placebo	Prednisolone administration may improve pregnancy outcomes in women with idiopathic RM

American Journal of Reproductive Immunology			RR 1.58 (95% CI 1.23 to 2.02), 2 RCT's, n=176	
Anticoagulant/ antiplatelet interventions				
Low-molecular-weight heparin plus aspirin versus aspirin alone in pregnant women with hereditary thrombophilia to improve live birth rate: meta-analysis of randomized controlled trials Areia 2015 Archives of Gynaecology and Obstetrics	4	222	**Population: Pregnant women with hereditary thrombophilia** <u>Outcome: Miscarriage</u> 1) Low molecular weight heparin + Aspirin vs Aspirin alone OR 0.69 (95% CI 0.22 to 2.16), 4 RCTs, n=222 VERY LOW quality evidence <u>Outcome: Live birth</u> 1) Low molecular weight heparin + Aspirin vs Aspirin alone OR 1.70 (95%CI 0.72 to 4.0), 4 RCT's, n=222 VERY LOW quality evidence	Insufficient evidence to draw any recommendations. There is a need for large high quality RCT with homogenous inclusion criteria.

Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia De Jong 2014 Cochrane	9	1228	**Population: Pregnant women with 2 or more unexplained miscarriages with or without inherited thrombophilia** <u>Outcome: Live birth</u> 1) Aspirin vs no treatment RR 0.94 (95% CI 0.80 to 1.11), 2 RCTs, n=256 MODERATE quality evidence. 2) Low molecular weight heparin vs aspirin (excluding high risk of bias studies) RR 1.08 (95% CI 0.93 to 1.26), 2 RCTs, n = 239 LOW quality evidence 3) Low molecular weight heparin vs aspirin (including high risk of bias studies) RR 1.16 (95% CI 0.93 to 1.45), 3 RCTs, n=325 LOW quality evidence 4) Low molecular weight heparin vs no treatment RR 1.00 (95% CI 0.56 to 1.79), 1 RCT, n=6 LOW quality evidence 5) Low molecular weight heparin vs no treatment (including high risk of bias studies) RR 1.23 (95% CI 0.84 to 1.81), 3 RCTs, n=453 VERY LOW quality evidence 6) Low molecular weight heparin and aspirin vs no-treatment RR 1.01 (95% CI 0.87 to 1.16), 2 RCTs, n = 322	The effect of anticoagulants in women with unexplained recurrent miscarriage and inherited thrombophilia needs to be assessed in further randomised controlled trials; at present there is no evidence of a beneficial effect.

			HIGH quality evidence 7) Low molecular weight heparin and aspirin versus aspirin RR 1.11 (95% CI 0.94 to 1.30), 2 RCTs, n=327 MODERATE quality evidence 8) Low molecular weight heparin and aspirin vs Low molecular weight heparin RR 0.91 (95% CI 0.72 to 1.15), 1 RCT, n=126 LOW quality evidence 9) Low molecular weight heparin with or without aspirin vs no treatment (including studies at high risk of bias) RR 1.07 (95% CI 0.99 to 1.15), 5 RCTs, n=793 LOW quality evidence 10) Low molecular weight heparin with or without aspirin vs no treatment RR 0.98 (95% CI 0.85 to 1.12), 3 RCTs, n=324 HIGH quality evidence	
Comparison of therapeutic interventions for recurrent pregnancy loss in association with antiphospholipid syndrome: a systematic	12	1910	**Population: Pregnant women with 2 or more consecutive pregnancy loss's and antiphospholipid syndrome** <u>Outcome: Live birth</u> 1) Aspirin vs Low molecular weight heparin + Aspirin OR 0.37 (95% CI 0.17 to 0.71), 3 RCT's, n=1201 LOW quality evidence	Heparin plus aspirin is recommended for women with recurrent pregnancy loss and APS. Large RCT's are needed to

review and network meta-analysis Liu 2020 American Journal of Reproductive Immunology			2) Unfractionated heparin + aspirin vs Low molecular weight heparin + Aspirin OR 0.90 (95% CI 0.36 to 1.83), 3 RCT's, n=136 LOW quality evidence 3) Low molecular weight heparin vs Low molecular weight heparin + aspirin OR 1.36 (95% CI 0.15 to 5.49), * LOW quality evidence 4) Placebo vs Low molecular weight heparin + aspirin OR 0.77 (95% CI 0.17 to 2.22), 1 RCT, n=180 LOW quality evidence 5) Unfractionated heparin + aspirin vs aspirin OR 2.63 (95% CI 1.04 to 5.39), 3 RCT's, n=212 LOW quality evidence 6) Low molecular weight heparin vs aspirin OR 3.70 (95% CI 0.51 to 13.51), 1 RCT, n=141 LOW quality evidence 7) Placebo vs aspirin OR 2.31 (95% CI 0.47 to 6.63), 1 RCT, n=40 LOW quality evidence 8) Low molecular weight heparin vs Unfractionated heparin + aspirin OR 1.76 (95% CI 0.17 to 6.45), * LOW quality evidence	explore the potential therapeutic efficacy and safety differences between Unfractionated heparin and Low molecular weight heparin when combined with aspirin.

			9) Placebo vs Unfractionated heparin + aspirin OR 1.04 (95% CI 0.16 to 3.64), * LOW quality evidence 10) Placebo vs Low molecular weight heparin OR 1.50 (0.09 to 5.32), * LOW quality evidence * No direct comparisons	
Antithrombotic Treatment for Recurrent Miscarriage: Bayesian Network meta-analysis and systematic review Zhang 2015 Medicine	19	2391 recurrent miscarriage women with or without thromb-ophilia. 543 recurrent miscarriage women with APS	**Population: Women with 2 or more miscarriages of unknown cause with or without thrombophilia** <u>Outcome: Live birth</u> 1) Low molecular weight heparin alone (85.1%) 2) Low molecular weight heparin + Aspirin (69.7%) 3) Placebo alone (38.1%) 4) Aspirin alone (7.1%) [Ranking amongst available treatments) Intervention (SUCRA)] **Population: Women with 2 or more miscarriages of unknown cause apart from Antiphospholipid syndrome (APS)** <u>Outcome: Live birth</u> 1) Unfractionated heparin + Aspirin (75.5%) 2) Low molecular weight heparin alone (71%) 3) Placebo alone (47.7%) 4) Low molecular weight heparin + Aspirin (34.4%) 5) Aspirin alone (23%)	Results do not support the use of combined LMWH and aspirin for recurrent miscarriage treatment, and suggest aspirin may have negative effects for lowering the risk of pregnancy loss.

			[Ranking amongst available treatments) Intervention (SUCRA)] Unable to GRADE assess. There is a low risk of bias in >50% of the included studies.	
Hormonal/ endocrine interventions				
A systematic review of dydrogesterone for the treatment of recurrent miscarriage Carp 2015 Gynaecological Endocrinology	2	509	**Population: Women with 3 or more miscarriages** <u>Outcome: Miscarriage</u> 1) Dydrogesterone vs control OR 0.35 (95% CI 0.19 to 0.65), 2 RCTs, n=509 MODERATE quality evidence	Evidence suggests benefit in reducing miscarriage risk with oral dydrogesterone.
Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear aetiology Haas 2019	12	1856	**Population: Women with recurrent miscarriage of unclear aetiology** <u>Outcome: Miscarriage</u> 1) Progestogen vs placebo/ no treatment RR 0.73 (95% CI 0.54 to 1.00), 10 RCTs, n=1684 MODERATE quality evidence <u>Outcome: Live birth</u> 1) Progestogen vs placebo/ no treatment	For women with unexplained recurrent miscarriages, supplementation with progestogen therapy may reduce the rate of miscarriage in

Cochrane			RR 1.07 (95% CI 1.00 to 1.13), 6 RCTs, n=1411 MODERATE quality evidence	subsequent pregnancies.
Combined oestrogen and progesterone for preventing miscarriage Lim 2013 Cochrane	2	281	**Population: Women with long history of diabetes** <u>Outcome: Miscarriage</u> 1) Oestrogen + progestogen vs placebo RR 0.95 (95% CI 0.32 to 2.80), 1 RCT, n=148 LOW quality evidence **Population: Pregnant women having undergone IVF** <u>Outcome: Miscarriage</u> 1) Oestrogen + progesterone vs no treatment RR 0.66 (95% CI 0.23 to 1.85), 1 RCT, n=118 VERY LOW quality evidence NB. Authors felt it inappropriate to perform meta-analysis due to significant heterogeneity between trials in terms of population, intervention, control, definition of miscarriage, trial design and trial methodology	Insufficient evidence to assess the use of combined oestrogen and progesterone for preventing miscarriages. We strongly recommend further research in this area.
Human chorionic gonadotrophin (hCG) for	5	596	**Population: Women with a history of unexplained recurrent miscarriage (>3 consecutive pregnancy losses)** <u>Outcome: Miscarriage</u>	The evidence supporting hCG supplementatio n to prevent recurrent

preventing miscarriage Morley 2013 Cochrane			1) Human chorionic gonadotrophin vs No treatment/ placebo (all studies) RR 0.51 (95% CI 0.32 to 0.81), 5 RCT's, n=302 LOW quality evidence 2) Human chorionic gonadotrophin vs No treatment/ placebo (low risk of bias studies only) RR 0.74 (95% CI 0.44 to 1.23). 3 RCT's, n=254 LOW quality evidence	miscarriage remains equivocal. A well-designed randomised controlled trial of adequate power and methodological quality is required.
Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history Chen 2016 Cochrane	1	46	**Population: Women with idiopathic hyperprolactinaemia and a history of recurrent miscarriage.** <u>Outcome: Miscarriage</u> 1) Oral bromocriptine vs No treatment RR 0.28 (95% CI 0.09 to 0.87), 1 RCT, n=46 LOW quality evidence <u>Outcome: Live birth</u> 1) Oral bromocriptine vs No treatment RR 1.50 (95% CI 0.93 to 2.42), 1 RCT, n=46 VERY LOW quality evidence	Insufficient evidence to evaluate the effectiveness of dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and a history of recurrent miscarriage. Further high-quality research

				in this area is warranted.
Interventions for hyperthyroidism pre-pregnancy and during pregnancy Earl 2013 Cochrane	0	0	**Population: Women with hyperthyroidism before or during pregnancy** 1) Antithyroid interventions vs Other intervention/ no intervention/ placebo There are no trials assessing interventions for hyperthyroidism pre-pregnancy or during pregnancy.	More observational research is required about the potential harms of methimazole in early pregnancy and about the potential liver damage from propylthiouracil.
Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity Rao 2019	8	1825	**Population: Pregnant women with subclinical hypothyroidism (SCH)** <u>Outcome: Miscarriage</u> 1) Levothyroxine (LT4) vs No treatment/ placebo RR 0.27 (95% CI 0.14 to 0.52), 3 RCTs, n=500 MODERATE quality evidence **Population: Pregnant women with thyroid autoimmunity (TAI)** <u>Outcome: Miscarriage</u> 1) Levothyroxine (LT4) vs No treatment/ placebo RR 0.68 (95% CI 0.48 to 0.97), 5 RCTs, n=1325 HIGH quality evidence	The evidence suggests levothyroxine supplementation may reduce the risks of pregnancy loss among pregnant women with SCH and/or TAI. However, this review does not include data from the largest RCT on the

Human Reproduction Update				subject, TABLET trial (Dhillon-Smith 2019) (203).
Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy Reid 2013 Cochrane	1	169	**Population: Women with hypothyroidism or subclinical hypothyroidism that are pregnant or during pre-pregnancy** <u>Outcome: Miscarriage</u> 1) Selenomethionine vs Placebo RR 0.85 (95% CI 0.30 to 2.42), 1 RCT, n=169 VERY LOW quality evidence (Data on levothyroxine vs placebo/no treatment is outdated, latest in Rao et al 2019)	Insufficient evidence to recommend selenium supplementation in women with subclinical hypothyroidism. Further studies needed in this area.
Insulin sensitising interventions				
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo	6	798	**Population: Women with polycystic ovary syndrome, oligo amenorrhoea and subfertility** <u>Outcome: Miscarriage</u> 1) Metformin vs No treatment/ placebo OR 1.08 (95% CI 0.50 to 2.35), 4 RCTs, n=748 LOW quality evidence. <u>Outcome: Live birth</u>	Metformin alone may have a beneficial effect over placebo for live birth. Future studies should stratify by body-mass-index. This review should

amenorrhoea and subfertility. Morley 2017 Cochrane			1) Metformin vs No treatment/ placebo OR 1.59 (95% CI 1.00 to 2.51). 4 RCT's, n=435 LOW quality evidence **Population: Women with polycystic ovary syndrome** <u>Outcome: Miscarriage</u> 1) Metformin + Clomiphene vs Clomiphene OR 1.59 (95% CI 1.03 to 2.46), 9 RCTs, n=1529 LOW quality evidence 2) Metformin vs Clomiphene OR 0.92 (95% CI 0.50 to 1.67), 5 RCTs, n=741 VERY LOW quality evidence. <u>Outcome: Live birth</u> 1) Metformin + Clomiphene vs Clomiphene OR 1.21 (95% CI 0.92 to 1.59), 9 RCTs, n=1079 LOW quality evidence 2) Metformin vs Clomiphene OR 1.71 (95% CI 1.00 to 2.94), 3 RCTs, n=241 VERY LOW quality evidence.	be updated to include the findings from the PregMet2 trial (Lovvik 2019).
Effect of pre-conceptional metformin on abortion risk in	17	566	**Population: Women with polycystic ovary syndrome (PCOS)** <u>Outcome: Miscarriage</u>	Metformin has no effect on the miscarriage risk in PCOS patients

polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Palomba 2009 Fertility and Sterility			1) Metformin (started pre-conceptional) vs No metformin OR 0.89 (95% CI 0.65 to 1.21), 17 RCTs, n=566 No full risk of bias assessment done for individual studies performed, therefore unable to perform overall GRADE assessment	when administered before pregnancy. A large high quality RCT commencing metformin preconception and continuing throughout first trimester is needed.
Cervical cerclage interventions				
Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy Alfirevic 2017 Cochrane	12	2642	**Population: Women with a singleton pregnancy at high risk of a miscarriage (due to history, short cervix on ultrasound or determined by physical examination)** <u>Outcome: Miscarriage (loss before 24 weeks)</u> 1) Cerclage vs No cerclage RR) 0.84 (95% CI 0.58 to 1.22), 7 RCT's, n=2091 MODERATE quality evidence 2) Cerclage vs Vaginal progesterone RR 0.58 (95% CI 0.17 to 2.01), 2 RCT's, n=128 MODERATE quality evidence 3) Cerclage vs Intramuscular progesterone RR 1.47 (95% CI 0.38 to 5.73), 1 RCT, n=79	Whether cerclage is more or less effective than other preventative treatments e.g. vaginal progesterone, remains unanswered.

			MODERATE quality evidence 4) History indicated cerclage vs Ultrasound-indicated cerclage RR 1.71 (95% CI 0.55 to 5.30), 2 RCT's, n=344 MODERATE quality evidence	
Surgical interventions				
Septum resection for women of reproductive age with a septate uterus Rikken 2017 Cochrane	0	0	**Population: Women of reproductive age with a septate uterus** 1) Hysteroscopic septal resection vs No treatment There are no published trials on hysteroscopic septum resection in women with a septate uterus	At present, there is no evidence to support the surgical procedure in these women. Randomised controlled trials are urgently needed. Two trials are currently underway.
Endometrial injury interventions				
Endometrial injury for pregnancy following sexual intercourse or intrauterine insemination (IUI)	6 4 (IUI) 2 (SI)	1512	**Population: Subfertile women and couples attempting to conceive through sexual intercourse (SI) or intrauterine insemination (IUI)** <u>Outcome: Miscarriage</u> 1) Intentional endometrial injury vs No intervention or sham procedure RR 0.73 (95% CI 0.38 to 1.39), 6 RCT's, n=174 VERY LOW quality evidence	Insufficient evidence to say whether endometrial injury improves the probability of live birth in women undergoing IUI

Lensen 2016 Cochrane			**Population: Subfertile women and couples attempting to conceive through sexual intercourse (SI)** <u>Outcome: Live birth</u> 1) Intentional endometrial injury vs No intervention or sham procedure RR 2.48 (95% CI 1.12 to 5.49), 2 RCTs, n=380 VERY LOW quality evidence	or attempting to conceive via sexual intercourse. Further large good quality RCTs needed in this area.
Lifestyle interventions				
Bed rest during pregnancy for preventing miscarriage Aleman 2005 Cochrane	2	84	**Population: Pregnant women at high risk of miscarriage (women with either a previous history of miscarriage (fewer than three consecutive miscarriages) or threatened miscarriage in the current pregnancy)** <u>Outcome: Miscarriage</u> 1) Bed rest vs Human chorionic gonadotrophin RR 2.50 (95% Ci 1.22 to 5.11), 1 RCT, n=40 VERY LOW quality evidence 2) Bed rest vs No bed rest (placebo and activity) RR 1.54 (95% CI 0.92 to 2.58), 2 RCTs n=64 VERY LOW quality evidence 3) Bed rest at home vs No bed rest (placebo and activity) RR 1.66 (95% CI 0.99 to 2.77), 2 RCTs, n=57 VERY LOW quality evidence 4) Bed rest in hospital vs No bed rest (activity or placebo or other treatment)	Insufficient evidence of high quality that supports a policy of bed rest in order to prevent miscarriage.

			RR 0.42 (95% CI 0.02 to 8.91), 1 RCT, n=16 VERY LOW quality evidence	
Antenatal interventions for reducing weight in obese women for improving pregnancy outcome. Furber 2013 Cochrane	0	0	**Population: Women who are pregnant and obese** 1) Weight-loss intervention vs Routine care/ More than one weight loss intervention There were no trials designed to reduce weight in obese pregnant women	Further studies are required to explore the potential benefits, or harm, of weight loss in pregnancy when obese before weight loss interventions in pregnancy can be designed.
Micronutrient intervention				
Vitamin supplementation for preventing miscarriage Balogun 2016 Cochrane	16	109,691	**Population: Pregnant women** <u>Outcome: Miscarriage (early or late)</u> 1) Vitamin C + Vitamin E vs control RR 0.90 (95% CI 0.65 to 1.26), 4 RCTs, n=13,346 MODERATE quality evidence 2) Vitamin A + Iron + Folate vs Iron + Folate RR 0.86 (95% CI 0.46 to 1.62), 2 RCTs, n=1397 LOW quality evidence	Taking any vitamin supplements prior to pregnancy or in early pregnancy does not prevent women experiencing miscarriage. There is

			3) Multivitamin + Iron + Folate vs Iron + Folate RR 0.98 (95% CI 0.94 to 1.03), 10 RCTs, n=94,948 MODERATE quality evidence 4) Vitamin C vs no supplement/ placebo RR 1.17 (95% CI 0.52 to 2.65), 2 RCTs, n=224 5) Vitamin A vs placebo RR 0.98 (95% CI 0.92 to 1.04), 1 RCT, n=39,668 6) Beta-carotene vs placebo RR 1.00 (95% CI 0.94 to 1.06), 1 RCT, n=39,668 7) Multivitamin without folate vs No multivitamin or folate RR 0.89 (95% CI 0.59 to 1.34), 1 RCT, n=907 8) Multivitamin + folate vs Folate RR 0.97 (95% CI 0.80 to 1.18), 3 RCTs, n=5012 9) Multivitamin + folate vs No multivitamin or folate RR 0.99 (95% CI 0.72 to 1.38), 3 RCTs, n=6883	insufficient evidence to examine the effects of different combinations of vitamins on miscarriage and miscarriage-related outcomes.
Effects and safety of peri-conceptional folate supplementation for preventing birth defects	5	7391	**Population: Women who were 12 weeks of gestation or less** <u>Outcome: Miscarriage</u> 1) Folate vs No intervention/ placebo/ other micronutrients without folate RR 1.10 (95% CI 0.94 to 1.28), 5 RCTs, n=7391	There is no evidence of any preventive or negative effects on pregnancy loss.

De-Regil 2015 Cochrane			MODERATE quality evidence	
Multiple-micronutrient (MMN) supplementation for women during pregnancy Keats 2019 Cochrane	12	107,220	**Population: Women who were 12 weeks of gestation or less** <u>Outcome: Miscarriage (loss before 28 weeks)</u> 1) Multiple micronutrients + Iron + Folic acid vs Iron +/- Folic acid RR 0.99 (95% CI 0.94 to 1.04), 12 RCTs, n=107,220 HIGH quality evidence	No evidence of benefit in reducing miscarriage with MMN supplementation in addition to iron +/- folic acid.
Complementary interventions				
Chinese herbal medicines for unexplained recurrent miscarriage Li 2016 Cochrane	7	691	**Population: Women with unexplained recurrent miscarriage (≥2 consecutive miscarriages before 20 weeks gestation)** <u>Outcome: Live birth</u> 1) Chinese herbal medicines vs Other pharmaceuticals RR 1.05 (95% CI 0.67 to 1.65), 1 RCT, n=80 VERY LOW quality evidence 2) Combination of Chinese herbal medicines + other pharmaceuticals vs Other pharmaceuticals alone: RR 1.55 (95% CI 1.14 to 2.10). 6 RCT's, n=601	Limited evidence to assess the effectiveness of Chinese herbal medicines for treating unexplained recurrent miscarriage. High-quality studies are

			VERY LOW quality evidence 3) Combination of Chinese herbal medicines + Psychotherapy vs Psychotherapy alone RR 1.32 (95% CI 1.07 to 1.64), 1 RCT, n=90 VERY LOW quality evidence	needed to further evaluate the effectiveness and safety of Chinese herbal medicines for unexplained recurrent miscarriage and should also consider safety issues for mother and baby.
Chinese herbal medicine for the treatment of recurrent miscarriage: a systematic review of RCTs Yang 2013 BMC Complementary and Alternative Medicine	16	1023	**Population: Women with recurrent miscarriage** <u>Outcome: Live birth</u> 1) Chinese herbal medicine vs Progesterone-based treatment RR 1.31 (95% CI 1.13 to 1.52), 4 RCTs, n=481 MODERATE quality evidence 2) Chinese herbal medicine vs Progesterone + Human chorionic gonadotrophin-based treatment RR 1.25 (95% CI 1.06 to 1.47), 1 RCT, n=158 VERY LOW quality evidence 3) Chinese herbal medicine vs Conventional medicine with uncertain effect RR 0.97 (95% CI 0.41 to 2.33), 3 RCTs, n=214	Some Chinese herbal medicines or in combination with progesterone-based treatment, may have beneficial effect on increasing live birth rate. Further clinical evidence of robust design is

			4) Chinese herbal medicine + Conventional medicine vs Progesterone-based treatment alone RR 1.17 (95% CI 1.07 to 1.29), 4 RCTs, n=75 LOW quality evidence 5) Chinese herbal medicine + Conventional medicine vs Human chorionic gonadotrophin-based treatment RR 1.20 (95% CI 1.01 to 1.43), 1 RCT, n=75 6) Chinese herbal medicine + Conventional medicine vs progesterone + Human chorionic gonadotrophin-based treatment RR 1.08 (95% CI 0.93 to 1.25), 3 RCTs, n=148 VERY LOW quality evidence 7) Chinese herbal medicine + Conventional medicine vs Conventional medicine with uncertain effect RR 1.55 (95% CI 1.16 to 2.08), 5 RCTs, n=485 LOW quality evidence	warranted to evaluate the efficacy and safety of Chinese herbal medicines for the treatment of recurrent miscarriage.
Any other interventions				
Interventions for treating hyperemesis gravidarum Boelig 2016 Cochrane	4	252	**Population: Pregnant women with hyperemesis gravidarum** <u>Outcome: Miscarriage</u> 1) Acupuncture and Acupressure vs Placebo RR 0.48 (95% CI 0.05 to 5.03), 1 RCT, n=57 LOW quality evidence 2) Midwife-led outpatient care vs Routine care RR 0.96 (95% CI 0.15 to 6.34), 1 RCT, n=53 LOW quality evidence	No suggestion of harm or benefit with acupuncture, acupressure, midwife led outpatient care, corticosteroids or ACTH on

			3) Corticosteroids vs Placebo RR 0.64 (95% CI 0.11 to 3.70), 1 RCT, n=110 VERY LOW quality evidence 4) Adrenocorticotropic hormone (ACTH) vs Placebo RR 1.00 (95% CI 0.07 to 14.64), 1 RCT, n=32 VERY LOW quality evidence	miscarriage outcome.
Antibiotics for treating bacterial vaginosis in pregnancy Brocklehurst 2013 Cochrane	2	1270	**Population: Pregnant women with bacterial vaginosis or intermediate vaginal flora whether symptomatic or asymptomatic and detected through screening** <u>Outcome: Miscarriage (late)</u> 1) Clindamycin (oral) vs Placebo RR 0.20 (95% CI 0.04 to 0.89), 1 RCT, n=485 MODERATE quality evidence 2) Clindamycin (vaginal) vs No treatment RR 0.20 (95% CI 0.01 to 4.10), 1 RCT, n=785 LOW quality evidence	Antibiotic treatment can eradicate bacterial vaginosis in pregnancy and oral Clindamycin treatment reduces risk of late miscarriage.
Giving women their own case notes to carry during pregnancy Brown 2015	1	212	**Population: Pregnant women** <u>Outcome: Miscarriage</u> 1) Carrying full set of antenatal records vs Carrying “co-op” card (full maternity notes retained by hospital) RR 1.19 (95% CI 0.45 to 3.16), 1 RCT, n=212	There is no evidence to suggest reduction in miscarriage by women carrying

Cochrane			VERY LOW quality evidence	their pregnancy case notes.
Pharmacological interventions for promoting smoking cessation during pregnancy Claire 2020 Cochrane	4	1782	**Population: Pregnant women who smoke** <u>Outcome: Miscarriage</u> 1) Nicotine replacement therapy (NRT) vs Placebo + Similar/ matched behavioural support or Similar/ matched behavioural support only RR 1.60 (95% CI 0.53 to 4.83), 5 RCTs, n=1916 LOW quality evidence	There was insufficient evidence to conclude whether nicotine replacement therapy had either positive or negative impacts on rates of miscarriage.
Mefloquine for preventing malaria in pregnant women Gonzales 2018 Cochrane	2	450	**Population: Pregnant women** <u>Outcome: Miscarriage</u> 1) Mefloquine vs Cotrimoxazole RR 1.07 (95% CI 0.07 to 16.84), 1 RCT, n=139 VERY LOW quality evidence 2) Mefloquine vs Placebo RR 0.48 (95% CI 0.04 to 5.22), 1 RCT, n=311 VERY LOW quality evidence	There is no evidence of any increased or decreased risk of miscarriage with mefloquine treatment.

Table 17: Miscarriage and live birth outcomes from included systematic reviews looking at asymptomatic women

Prevention of miscarriage in symptomatic women

Five reviews looked at interventions to prevent miscarriage in symptomatic women. Symptomatic women were defined as women who have experienced bleeding in pregnancy and therefore, had a threatened miscarriage. The full results from all included reviews are presented in Table 18.

Hormonal and endocrine interventions

Four reviews (Carp 2012, Devaseelan 2010, Lee 2017, Wahabi 2018) looked at hormonal and endocrinological interventions (204–207). Carp 2012 looked at dydrogesterone in women with threatened miscarriage and compared it to bed rest or vitamin supplementation or placebo and found benefit with meta-analysis of five trials (OR 0.47; 95% CI 0.31, 0.70) for miscarriage. We were unable to perform a GRADE assessment or a summary risk of bias for this comparison as individual risk of bias assessments for the contributory trials were not presented. Lee 2017 also looked at oral dydrogesterone and similar to Carp 2012, found low-quality evidence of benefit compared to conservative treatment (OR 0.43; 95% CI 0.26, 0.71). They also found low-quality evidence of benefit when comparing any progesterone formulation to placebo or conservative treatment (OR 0.53; 95% CI 0.36, 0.78) from seven RCTs. However, when specifically looking at vaginal progesterone they found high-quality evidence of no benefit when compared to placebo or conservative treatment (OR 0.72; 95% CI 0.39, 1.34) in four RCTs. Wahabi 2018 also looked at progesterone for miscarriage. They found moderate-quality evidence of benefit for any progesterone when compared to placebo or no treatment (RR 0.64; 95% CI 0.47, 0.87) from seven RCTs and moderate-quality evidence

of benefit from three RCTs when comparing oral progesterone to no treatment (RR 0.57; 95% CI 0.38, 0.85). However, they found moderate-quality evidence of no benefit for vaginal progesterone when compared to placebo (RR 0.75; 95% CI 0.47, 1.21) from four RCTs. Overall, therefore, progesterone appears to have some benefit for reducing miscarriage in women with threatened miscarriage, particularly oral preparations. This is reflected in the authors recommendations from each of the three reviews which looked at progesterone.

Devaseelan 2010 looked at hCG in women with a threatened miscarriage and found moderate-quality evidence of benefit compared to bed rest (RR 0.47; 95% CI 0.27, 0.82) but low-quality evidence of no benefit when compared to placebo (RR 0.83; 95% CI 0.46, 1.47), both from two RCTs each. The authors concluded that there was not enough evidence for the routine use of hCG to improve pregnancy outcomes and further good-quality RCTs are needed to assess its use in this population.

Complementary interventions

Li 2012 was the only included review to look at complementary interventions and their effect on the continuation of a pregnancy after 28 weeks' gestation, which we present as an outcome inversely related to miscarriage (208). They found very-low-quality evidence from a single RCT of no benefit of Chinese herbal medicine (CHM) compared to western medicines from one RCT (RR 1.23; 95% CI 0.96, 1.57). However, for CHM plus western medicines versus western medicines alone, moderate-quality evidence from five RCTs did suggest benefit (RR 1.28; 95%

CI 1.18, 1.38). The authors felt further high-quality research is needed looking at CHM alone with this population.

Article, author, year of publication and journal	Number of trials with data for miscarriage or live birth	Total number of partici-pants in the meta-analysis	Summary findings for outcomes of miscarriage and live birth and assessment for quality of evidence	Implications for practice or research
Hormonal/ endocrine interventions			vs: versus, OR: Odds ratio, RR: Risk ratio, CI: Confidence interval, NS: Not significant, RCT: Randomised controlled trial, n: Number of participants in that comparison	
A systematic review of dydro-gesterone for the treatment of threatened miscarriage Carp 2012.	5	660	**Population: Women with threatened miscarriage** <u>Outcome: Miscarriage</u> 1) Dydrogesterone vs Bed rest/ Vitamin supplementation/ Placebo OR 0.47 (95% CI 0.31 to 0.70), 5 RCTs, n=660 Unable to perform GRADE assessment	To consider use of dydrogesterone in prevention of threatened miscarriage.
Human chorionic gonado-trophin for threatened miscarriage	3	303	**Population: Women with threatened miscarriage and a previously viable fetus** <u>Outcome: Miscarriage</u> 1) Human chorionic gonadotrophin vs Bed rest/ No treatment/ Placebo RR 0.66 (95% CI 0.42 to 1.05), 3 RCTs, n=303	Current evidence does not support the routine use of hCG in treatment of threatened miscarriage. Good quality

Deevaseelan 2010 Cochrane			MODERATE quality evidence 2) Human chorionic gonadotrophin vs Placebo RR 0.83 (95% CI 0.46 to 1.47), 2 RCTs, n=215 LOW quality evidence 1) Human chorionic gonadotrophin vs Bed rest RR 0.47 (95% CI 0.27 to 0.82), 2 RCTs, n=108 MODERATE quality evidence	RCT's are urgently needed to assess the effects of hCG in threatened miscarriage.
The Influence of Oral Dydrogesterone and Vaginal Progesterone on threatened abortion Lee 2017 BioMed Research International	7	777	**Population: Women with threatened miscarriage** <u>Outcome: Miscarriage</u> 1) Any progesterone vs Placebo/ Conservative OR 0.53 (95% CI 0.36 to 0.78),7 RCTs, n=777 LOW quality evidence 2) Oral dydrogesterone vs Conservative OR 0.43 (95% CI 0.26 to 0.71), 3 RCTs, n=491 LOW quality evidence 3) Vaginal progesterone vs Placebo/ Conservative OR 0.72 (95% CI 0.39 to 1.34), 4 RCTs, n=286 HIGH quality evidence	Progesterone therapy, especially oral dydrogesterone, may prevent miscarriage in pregnant women experiencing threatened abortion

Progestogen for treating threatened miscarriage Wahabi 2018 Cochrane	7	696	**Population: Women with threatened miscarriage** <u>Outcome: Miscarriage</u> 1) All progestogens vs Placebo / No treatment RR 0.64 (95% CI 0.47 to 0.87), 7 RCTs, n=696 MODERATE quality evidence 2) Oral progestogen vs No treatment RR 0.57 (95% CI 0.38 to 0.85), 3 RCTs, n=408 MODERATE quality evidence 3) Vaginal progesterone vs Placebo RR 0.75 (95% CI 0.47 to 1.21), 4 RCTs, n=288 MODERATE quality evidence	Progestogens are probably effective in the treatment of threatened miscarriage but may have little or no effect in the rate of preterm birth. This review does not include data from the recently published largest trial on the subject PRISM (Coomarasamy 2019).
Complementary interventions				
Chinese herbal medicines for threatened miscarriage Li 2012 Cochrane	6	610	**Population: Women with threatened miscarriage** <u>Outcome: The rate of continuation of pregnancy after 28 weeks</u> 1) Chinese herbal medicines vs Western medicines RR 1.23 (95% CI 0.96 to 1.57), 1 RCT, n=60 VERY LOW quality evidence 2) Chinese herbal medicines + Western medicines vs Western medicines alone RR 1.28 (95% CI 1.18 to 1.38), 5 RCTs, n=550	Insufficient evidence to assess the effectiveness of Chinese herbal medicines alone for treating threatened miscarriage. Furt her high quality

			MODERATE quality evidence	research is needed.

Table 18: Miscarriage and live birth outcomes from included systematic reviews looking at symptomatic women

Management of miscarriage

There were 13 reviews that looked at interventions to manage a miscarriage. The full results from all included reviews are presented in Table 19.

Management of first trimester miscarriage

Six reviews (Ghosh 2021, Al-Wattar 2019, Nanda 2012, Wen 2008, Wu 2017, Webber 2015) looked at the management of miscarriage in the first trimester (209–214). It should be noted that we included the network meta-analysis from chapter four of this thesis in this group. Ghosh 2021 performed a network meta-analysis and ranked interventions according to their SUCRA for the outcome of complete miscarriage. They found the highest-ranked intervention was suction aspiration plus cervical preparation (SUCRA 99.2%), dilatation and curettage (SUCRA 69.9%) ranked second, suction aspiration (SUCRA 58.5%) ranked third, mifepristone plus misoprostol (SUCRA 47.8%) ranked fourth, misoprostol (SUCRA 24.6%) ranked fifth and expectant management or placebo (SUCRA 0.0%) ranked last. However, the evidence was only of either low-quality or very-low-quality for all comparisons apart from mifepristone plus misoprostol for which it was moderate-quality.

This conflicted somewhat with Al-Wattar 2019 who performed a similar network meta-analysis on the same population of women with a miscarriage of less than or equal to 14 weeks of gestation. Al-Wattar 2019 found mifepristone plus misoprostol (SUCRA 89.3%) was the highest-ranked intervention for completing a miscarriage, electric vacuum aspiration under general anaesthesia was second (SUCRA 76.2%), sharp dilation and curettage ranked third

(SUCRA 51.1%), misoprostol plus electric vacuum aspiration under general anaesthesia ranked fourth (SUCRA 39.4%), manual vacuum aspiration under local anaesthesia ranked fifth (SUCRA 35.2%), misoprostol alone ranked sixth (SUCRA 34.8%) and expectant management ranked last (SUCRA 24.0%). GRADE assessment was not possible as the paired-wise meta-analyses were not presented by the authors but over 50% of included studies were judge to be at low or moderate risk of bias by the reviewers. The reasons for the differences between the two reviews, despite similar interventions, the same population and a large cross-over of included studies are not clear.

Nanda 2012 compared expectant management to surgical treatment for the same population of women as the previous two reviews. They found moderate-quality evidence, that surgical treatment was better than expectant management, for the outcome of miscarriage not complete by two weeks (RR 3.98; 96% CI 2.94, 5.38) from four RCTs. And similarly, they found moderate-quality evidence, that surgical treatment was better than expectant management for the outcome of miscarriage not complete by six to eight weeks (RR 2.56; 95% CI 1.15, 5.69) from three RCTs.

Wen 2008 compared manual vacuum aspiration to electric vacuum aspiration for the outcome of complete miscarriage and found low-quality evidence of no difference (RR 1.00; 95% CI 0.99, 1.02) from five RCTs.

Wu 2017 looked specifically at misoprostol for the missed miscarriage population instead of combining missed and incomplete miscarriage as one population in a network meta-analysis. For the outcome of complete miscarriage within 24 hours, they found sublingual misoprostol 600 micrograms (SUCRA 92.7%) ranked first, vaginal misoprostol 800 micrograms (SUCRA 88.4%) ranked second, vaginal misoprostol 600 micrograms (SUCRA 67.8%) ranked third, vaginal misoprostol 400 micrograms (SUCRA 36.7%) ranked fourth, sublingual misoprostol 400 micrograms (SUCRA 30.6%) ranked fifth, vaginal misoprostol 200 micrograms (SUCRA 23.0%) ranked sixth and oral misoprostol 400 micrograms (SUCRA 10.8%) ranked last. GRADE assessment was not possible as the paired-wise meta-analyses were not presented but over 50% of the included studies were judged to be at low or moderate risk of bias by the reviewers.

Webber 2015 looked at the outcome of the need for manual cervical dilation in women undergoing dilatation and curettage or vacuum aspiration for a miscarriage at less than 14 weeks gestation. They found very-low-quality evidence that any cervical preparation was better than placebo (RR 0.25; 95% CI 0.07 to 0.89) from two RCTs. They also found that misoprostol was better than placebo (RR 0.14; 95% CI 0.08, 0.26) from a single RCT. However, no difference was found when they compared isosorbide mononitrate or dinitrate to misoprostol (RR 0.76; 95% CI 0.10, 5.64). This evidence was of very-low-quality from three RCTs.

Overall, apart from the Al-Wattar 2019 review, the two reviews looking at multiple interventions agreed that for achieving a complete miscarriage, surgical interventions were

better than other inventions. All three agreed that expectant management is probably the worst at completing a miscarriage. The reasons for different results from Ghosh 2021 and Al-Wattar 2019 are likely to be multi-factorial. The two reviews had different numbers of nodes and as a result, different definitions for the interventions. The Ghosh 2021 review was also more recent and more comprehensive, utilising the methodological strength required by the robust Cochrane editorial process. The search was more extensive and carried out by a Cochrane information scientist and all data extraction and analysis was duplicated and then checked again to ensure accuracy by reviewers working independently. It was noted there was a lack of adequate supplementary information in the Al-Wattar 2019 review to perform a true comparison to discern other reasons for difficulties. Attempts were made to contact the corresponding author but no response was forthcoming.

Management of second trimester miscarriage

Three reviews (Cleeve 2019, Dodd 2010, Lemmers 2019) looked at the management of miscarriage beyond the first trimester (215–217). Cleeve 2019 looked at women with an intrauterine fetal demise between 14- and 28-weeks' gestation and looked at the outcome of complete miscarriage within 24 hours and presented relative risks. They did not find evidence of the benefit of adding mifepristone to misoprostol compared to misoprostol (RR 1.18; 95% CI 0.91, 1.53) from one RCT, however, this evidence was of very-low-quality. They also looked at multiple comparisons of different doses and regimens of misoprostol. They found low-quality evidence of no difference between mifepristone followed by 200 micrograms misoprostol versus mifepristone followed by 400 micrograms misoprostol (RR 0.90; 95% CI

0.74, 1.10). They found very-low-quality evidence of no difference between 100 micrograms misoprostol compared to 200 micrograms misoprostol (RR 0.79; 95% CI 0.39, 1.63). However, they found moderate-quality evidence that 200 micrograms misoprostol was less efficacious than 400 micrograms misoprostol (RR 0.78; 95% CI 0.66, 0.92). And low-quality evidence that 400 micrograms misoprostol was more efficacious than 600 micrograms misoprostol (RR 0.90; 95% CI 0.80, 1.00). Looking at the use of a loading dose of misoprostol, they found low-quality evidence that 200 micrograms misoprostol was more efficacious than 600 micrograms misoprostol followed by 200 micrograms misoprostol (RR 0.74; 95% CI 0.56, 0.97). However, they found low-quality evidence of no difference between 400 micrograms misoprostol compared to 600 micrograms misoprostol followed by 200 micrograms misoprostol (RR 0.95; 95% CI 0.77, 1.18). All of these comparisons were for the outcome of complete miscarriage within 24 hours. Cleeve 2019 also looked at different routines of administration for the same outcome. They found no difference between oral misoprostol compared to sublingual misoprostol (RR 0.88; 95% CI 0.70, 1.11). They found possible benefit for oral misoprostol versus vaginal misoprostol (RR 0.78; 95% CI 0.68, 0.89) but no difference between vaginal misoprostol compared to sublingual misoprostol (RR 0.93; 95% CI 0.85, 1.03). However, all the evidence looking at routes of administration was from two RCTs which were of low-quality. The authors suggest that 400 micrograms every four hours given sublingually or vaginally maybe the most effective management option, but they were unable to conclude about the benefits of mifepristone.

Dodd 2010 looked at a slightly different population to Cleeve 2019. They looked at women with intrauterine fetal death in the second and trimester and also women having a termination for fetal anomalies in the same trimesters. They also looked at the same outcome of delivery within 24 hours, and only at medical treatments. They found low-quality evidence of no difference between vaginal misoprostol compared to gemeprost with or without oxytocin (RR 1.30; 95% CI 0.64, 2.62] from three RCTs. They found low-quality evidence of no difference between vaginal misoprostol and prostaglandin E_2 (RR 0.62; 95% CI 0.36, 1.04) from four RCTs, and very-low-quality evidence of no difference between vaginal misoprostol and prostaglandin F_{2alpha} (RR 1.07; 95% CI 0.28, 4.06) from three RCTs. Low-quality evidence was found of no difference between vaginal misoprostol and vaginal misoprostol plus luminaria (RR 0.96; 95% CI 0.47, 1.97) from one RCT. And similarly, low-quality evidence was found of no difference between vaginal misoprostol compared to vaginal misoprostol plus vaginal nitric oxide donor (RR 0.89; 95% CI 0.34, 2.33] from one RCT. Moderate quality evidence of no difference between vaginal misoprostol six-hourly dosing intervals compared to vaginal misoprostol 12-hourly dosing intervals (RR 0.87; 95% CI 0.62, 1.22) from two RCTs was found. Looking at different routes of administration, there was low-quality evidence that vaginal misoprostol was better than oral misoprostol (RR 0.37; 95% 0.15, 0.87) from six RCTs. However, there was low-quality evidence of no difference between combined oral plus vaginal misoprostol compared to vaginal misoprostol alone (RR 1.81; 95% CI 0.60, 5.50) from one RCT. Combined oral plus vaginal misoprostol was found to be more efficacious than oral misoprostol alone (RR 0.47; 95% CI 0.23, 0.96) from one RCT, which was of moderate-quality. Low-quality evidence showed sublingual misoprostol was better than vaginal misoprostol (RR 0.24; 95% CI 0.08, 0.74) from two RCTs. However, no difference was found between sublingual

misoprostol and oral misoprostol (RR 0.22; 95% CI 0.01, 4.99) from two RCTs. All of these comparisons were for delivery within 24 hours. The authors of the review felt overall that vaginal misoprostol in this population was more effective than oral misoprostol and misoprostol was as effective as other prostaglandin preparations.

Lemmers 2019 looked at a similar but not identical population as Dodd 2010 and Cleeve 2019. In particular, they looked at women with early fetal death at less than 24 weeks gestation and looked at expectant management, medical, and surgical treatment. There were 22 comparisons in total for the outcome of complete miscarriage and the full results are presented in Table 19 below. No difference was found for varying combinations of misoprostrol administered by different routes, doses and consistencies or when combined or compared with other medications such as mifepristone, methotrexate, oxytocin, gemeprost or expectant management. They did find that vaginal misoprostol was more effective than placebo (RR 4.23; 95% CI 3.01, 5.94) from five RCTs and more effective than expectant management (RR 1.25; 95% CI 1.09, 1.45) from one RCT and more effective than vaginal dinoprostone (RR 1.83; 95% CI 1.37, 2.46) from two RCTs. However, it was less effective than surgical evacuation of the uterus (RR 0.40; 95% CI 0.32, 0.50) from nine RCTs. Lower-dose buccal misoprostol regimen was found to be less effective than higher-dose buccal misoprostol regimen (RR 0.71; 95% CI 0.58, 0.86) from one RCT. Vaginal gemeprost was found to be less effective than surgical evacuation (RR 0.80; 95% CI 0.67, 0.96) from one RCT. Misoprostol given intravaginally and extra-amniotic was possibly more effective than vaginal misoprostol given normally (RR 1.10; 95% CI 1.00, 1.22) from one RCT.

Overall, the authors of the review concluded that medical treatment with vaginal misoprostol may be an acceptable alternative to surgical or expectant management but further research is needed to ascertain the optimal route and doses of medical treatments as well as the safety and side effect profiles.

Management of incomplete miscarriage

Two reviews (Kim 2017, Tunçalp 2010) looked specifically at the population of women with incomplete miscarriage (218,219). Kim 2017 looked at the outcome of complete miscarriage for multiple comparisons. No difference was found between the following comparisons; misoprostol versus expectant care (RR 1.23, 95% CI 0.72, 2.10) from two RCTs; vaginal misoprostol versus expectant care (RR 1.23; 95% CI 0.72, 2.10) from two RCTs; vaginal plus oral misoprostol versus surgery (RR 0.95; 95% CI 0.87, 1.04) from one RCT, vaginal misoprostol versus oral misoprostol (RR 0.94; 95% CI 0.76, 1.16) from one RCT; oral misoprostol 600 micrograms versus oral misoprostol 1200 micrograms (RR 1.00; 95% CI 0.93, 1.07) from two RCTs; oral mifepristone plus vaginal misoprostol versus surgery (RR 1.00; 95% CI 0.78, 1.27) from one RCT; sublingual misoprostol versus oral misoprostol (RR 0.99; 95% CI 0.94 to 1.05) from two RCTs. Kim 2017 did find that misoprostol was less effective than surgery (RR 0.96; 95% CI 0.94, 0.98) from 15 RCTs. This was consistent when sub-grouped by route of administration of misoprostol. The authors concluded that misoprostol and expectant care are both acceptable alternatives to surgical evacuation but long-term follow-up studies are needed to examine this area further.

Tunçalp 2010 compared vacuum aspiration to sharp metal curettage for multiple outcomes. They found very-low-quality evidence of no difference between the intervention and comparator for the need for re-evacuation (RR 1.50 ;95% CI 0.29, 7.83) from two RCTs which is a related outcome to efficacy.

It should be noted that the definition of the outcome of interest for this review, which was complete miscarriage, varied between the studies which the included reviews included. We accepted the definition of the outcome of complete miscarriage as stated by the included reviews which in turn accepted the definition of the outcome as stated by the contributory papers. The diagnosis of complete miscarriage was based on clinical history and examination or ultrasound scan confirmation of an empty uterus or negative pregnancy tests or a combination of these three.

Management of other miscarriage related complications

Two reviews (May 2007, Udoh 2016) did not look at the efficacy of interventions at completing a miscarriage, but instead looked at other miscarriage related complications such as need for antibiotics (220,221). May 2007 looked at women with incomplete miscarriage of any gestation who were not overtly infected. They found low-quality evidence of no difference between oral tetracycline plus surgical evacuation and surgical evacuation without antibiotics (RR 1.61 ;95% CI 0.79 to 3.26) from one RCT and so the authors of the review concluded there was not enough evidence to evaluate the routine use of antibiotic prophylaxis in women with incomplete miscarriage.

Udoh 2016 looked at women with a septic miscarriage. For the outcome of reduction in fever they found moderate-quality evidence that there was no difference between clindamycin and penicillin plus chloramphenicol (Mean Difference (MD) -12.30 ;95% CI -25.12, 0.52) from one RCT. For time to fever resolution, there was low-quality evidence of no difference between penicillin and chloramphenicol compared to cephalothin plus kanamycin (MD -2.30; 95% CI -17.31, 12.71) from one RCT. And low-quality evidence for the benefit of oral tetracycline compared to intravenous penicillin G (MD -5.03; 95% CI -5.77, -4.29) from one RCT. The authors of the review concluded that there was the need for further high-quality RCTs in this area.

Article, author, year of publication and journal in which it was published	Number of trials with data for outcomes of interest	Total number of participants in the meta-analysis	Summary findings for outcomes of interest and assessment for quality of evidence	Implications for practice or research
First trimester miscarriage management			vs: versus, OR: Odds ratio, RR: Risk ratio, MD: Mean difference, CI: Confidence interval, NS: Not significant, RCT: Randomised controlled trial, n: Number of participants in that comparison, mcg: Micrograms	
Methods for managing miscarriage: a network meta-analysis Ghosh 2021 Cochrane	54	10,915	**Population: Pregnant women with a miscarriage of <u>≤</u> 14 weeks gestation** [Ranking amongst available treatments) Intervention (SUCRA) GRADE assessment of quality of evidence compared to Expectant/ placebo] <u>Outcome: Complete miscarriage</u> 1) Suction aspiration + Cervical preparation (99.2%) VERY LOW 2) Dilatation and Curettage (69.9%) LOW 3) Suction aspiration (58.5%) LOW 4) Mifepristone + Misoprostol (47.8%) MODERATE 5) Misoprostol (24.6%) LOW 6) Expectant/ placebo (0.0%) NA <u>Outcome: Composite outcome of death or serious complications</u> In ranked order of effectiveness (i.e., death or serious complication ranging from least likely to most likely) 1) Dilatation and curettage (81.5%) LOW	Surgical management is the most effective method for management of miscarriage and also has the lowest chance of serious complication. The combination of mifepristone and misoprostol is more effective than misoprostol alone especially for missed miscarriage

			2) Misoprostol (57.9%) LOW 3) Suction curettage (53.1%) LOW 4) Mifepristone + misoprostol (45.6%) LOW 5) Expectant/ placebo (11.9%) NA	
Management of first-trimester miscarriage: a systematic review and network meta-analysis Al-Wattar 2019 Human Reproduction Update	46	9520	**Population: Pregnant women with a miscarriage of < 14 weeks gestation** Outcome: Complete evacuation of products of conception [Ranking amongst available treatments) Intervention (SUCRA)] 1) Mifepristone + Misoprostol (89.3%) 2) Electric vacuum aspiration under general anaesthesia (76.2%) 3) Sharp dilation and curettage (51.1%) 4) Misoprostol + electric vacuum aspiration under general anaesthesia (39.4%) 5) Manual vacuum aspiration under local anaesthesia (35.2%) 6) Misoprostol alone (34.8%) 7) Expectant management (24.0%) Unable to perform GRADE assessment Summary of risk of bias assessment showed >50% of the included studies are low-moderate for risk of bias.	Medical treatments for first-trimester miscarriage have similar effectiveness and side effects compared to surgery. The addition of mifepristone could increase the effectiveness of misoprostol and reduce side effects though evidence is limited due to inconsistency. Expectant management has lower effectiveness

				compared to other treatment options.
Expectant care versus surgical treatment for miscarriage Nanda 2012 Cochrane	7	1521	**Population: Women with miscarriage (spontaneous pregnancy loss at less than 14 weeks gestation), with either ultrasound evidence of retained tissue, or with a clinical diagnosis of inevitable miscarriage or incomplete miscarriage (where there could be uncertainty as to whether any tissue remains in the uterus). In addition, we included women with ultrasound evidence of non-viable pregnancies at less than 14 weeks gestation.** <u>Intervention & Comparator: Expectant care vs Surgical treatment</u> 1) Miscarriage not complete by 2 weeks RR 3.98 (96% CI 2.94 to 5.38), 4 RCTs, n=1263 MODERATE quality evidence 2) Miscarriage not complete by 6-8weeks RR 2.56 (95% CI 1.15 to 5.69), 3 RCTs, n=430 MODERATE quality evidence 3) Need for additional or unplanned surgery RR 7.35 (95% CI 5.04 to 10.72), 5 RCTs, n=1454 MODERATE quality evidence 4) Pelvic infection by 8 weeks RR 0.63 (95% CI 0.36 to 1.12), 7 RCTs, n=1514 HIGH quality evidence 5) Bleeding with need for transfusion RR 6.45 (95% CI 1.21 to 34.42), 3 RCTs, n=1205	The existing evidence does not indicate the superiority of either expectant care or surgical treatment. Future studies need to separate outcomes for pregnancies found to be non-viable by ultrasound examination (without bleeding or pain).

			HIGH quality evidence	
Manual versus electric vacuum aspiration for first-trimester abortion: a systematic review Wen 2008 British Journal of Obstetrics and Gynaecology	5	1000	**Population: Women with first trimester miscarriage** <u>Outcome: Complete evacuation rate</u> 1) Manual vacuum aspiration vs Electric vacuum aspiration RR 1.00 (95% CI 0.99 to 1.02), 5 RCTs, n=1000 LOW quality evidence	There is some evidence that manual vacuum aspiration is as effective and acceptable as electric vacuum aspiration and might be safer than electric vacuum aspiration
Misoprostol for medical treatment of missed abortion: a systematic review and network meta-analysis Wu 2017	18	1802	**Population: Women with a missed miscarriage of less than 14 weeks gestation** <u>Outcome: Complete miscarriage within 24 hours</u> 1) Sublingual misoprostol 600mcg (92.7%) 2) Vaginal misoprostol 800mcg (88.4%) 3) Vaginal misoprostol 600mcg (67.8%) 4) Vaginal misoprostol 400mcg (36.7%) 5) Sublingual misoprostol 400mcg (30.6%) 6) Vaginal misoprostol 200mcg (23.0%) 7) Oral misoprostol 400mcg (10.8%)	Sublingual misoprostol of 600mcg or vaginal misoprostol of 800mcg may be a good choice for the first dose. The ideal dose and medication

Nature Scientific Reports			[Ranking amongst available treatments) Intervention (SUCRA)] Unable to perform GRADE assessment. Summary of risk of bias assessment showed >50% of the included studies are moderate for risk of bias.	interval of misoprostol however needs to be further researched.
Cervical ripening before first trimester surgical evacuation for non-viable pregnancy Webber 2015 Cochrane	5	318	**Population: Women undergoing dilation and curettage or vacuum aspiration for non-viable pregnancy at less than 14 weeks' gestation.** <u>Outcome: Need for manual cervical dilation</u> 1) Isosorbide mononitrate/ dinitrate vs Misoprostol RR 0.76 (95% CI 0.10 to 5.64), 3 RCTs, n=150 VERY LOW quality evidence. 2) Misoprostol vs Placebo RR 0.14 (95% CI 0.08 to 0.26), 1 RCT, n=120 VERY LOW quality evidence. 3) Any cervical preparation vs Placebo RR 0.25 (95% CI 0.07 to 0.89), 2 RCTs, n=168 VERY LOW quality evidence.	Limited conclusions can be drawn. Further research should be powered to assess the rate of cervical and uterine injury between interventions. Future research should also guide clinicians in deciding whether the benefits of reduced manual cervical dilatation outweigh the risks of adverse effects

				associated with these agents (nausea, vomiting, headache, fever, diarrhoea and pain).
Second trimester miscarriage management				
A systematic review of the effectiveness, safety, and acceptability of medical management of intrauterine fetal death at 14-28 weeks of gestation Cleeve 2019 International Journal of Gynaecology and Obstetrics	16	1890	**Population: Women with intrauterine fetal demise between 14 and 28 weeks gestation** <u>Outcome: Complete miscarriage within 24hours</u> Relative risks (RR) presented 1) Mifepristone followed by misoprostol vs misoprostol alone RR 1.18 (95% CI 0.91 to 1.53), 1 RCT, n=27. VERY LOW quality evidence 2) Mifepristone followed by 200mcg misoprostol vs mifepristone followed by 400mcg misoprostol RR 0.90 (95% CI 0.74 to 1.10), 1 RCT, n=176 LOW quality evidence 3) 100mcg misoprostol vs 200mcg misoprostol RR 0.79 (95% CI 0.39 to 1.63), 2 RCTs, n=204 VERY LOW quality evidence 4) 200mcg misoprostol vs 400mcg misoprostol RR 0.78 (95% CI 0.66 to 0.92), 2 RCTs, n=263	Misoprostol 400 micrograms every 4 hours, sublingually or vaginally, may be effective. Unable to draw conclusions about the added benefit of mifepristone.

			MODERATE quality evidence 5) 400mcg misoprostol vs 600mcg misoprostol RR 0.90 (95% CI 0.8 to 1.0), 1 RCT, n=100 LOW quality evidence 6) 200mcg misoprostol vs 600mcg misoprostol followed by 200mcg misoprostol RR 0.74 (95% CI 0.56 to 0.97), 1 RCT, n=100 LOW quality evidence 7) 400mcg misoprostol vs 600mcg misoprostol followed by 200mcg misoprostol RR 0.95 (95% CI 0.77 to 1.18), 1 RCT, n=99 LOW quality evidence 8) Oral misoprostol vs Sublingual misoprostol RR 0.88 (95% CI 0.70 to 1.11), 2 RCTs, n=202 LOW quality evidence 9) Oral misoprostol vs Vaginal misoprostol RR 0.78 (95% CI 0.68 to 0.89), 2 RCTs, n=300 LOW quality evidence 10) Vaginal misoprostol vs Sublingual misoprostol RR 0.93 (95% CI 0.85 to 1.03), 2 RCTs, n=230 LOW quality evidence	

Misoprostol for induction of labour to terminate pregnancy in the 2nd or 3rd trimester for fetal anomaly or after intrauterine fetal death Dodd 2010 Cochrane	21	1848	**Population: Women undergoing induction of labour to terminate pregnancy in the second and third trimester following an intrauterine fetal death or for fetal anomalies** <u>Outcome: Achieving vaginal birth within 24 hours</u> 1) Vaginal misoprostol vs Oral misoprostol RR 0.37 (95% 0.15 to 0.87), 6 RCTs, n=507 LOW quality evidence 2) Vaginal misoprostol 6-hourly dosing intervals vs Vaginal misoprostol 12-hourly dosing intervals RR 0.87 (95% CI 0.62 to 1.22), 2 RCTs, n=363 MODERATE quality evidence 3) Vaginal misoprostol vs Gemeprost +/- Oxytocin RR 1.30 [95% CI 0.64 to 2.62], 3 RCTs, n=235 LOW quality evidence 4) Vaginal misoprostol vs Prostaglandin E_2 RR 0.62 (95% CI 0.36 to 1.04), 4 RCTs, n=251 LOW quality evidence 5) Vaginal misoprostol vs Prostaglandin F_{2alpha} RR 1.07 (95% CI 0.28 to 4.06), 3 RCTs, n=213 VERY LOW quality evidence 6) Vaginal misoprostol vs Vaginal misoprostol + Luminaria RR 0.96 (95% CI 0.47 to 1.97), 1 RCT, n=68 LOW quality evidence	The use of vaginal misoprostol in the termination of second and third trimester of pregnancy is as effective as other prostaglandin preparations (including cervagem, prostaglandin E_2 and prostaglandin F_{2alpha}), and more effective than oral administration of misoprostol. Future research should be directed towards determining the optimal dose and frequency of

			7) Vaginal misoprostol vs Vaginal misoprostol + Vaginal nitric oxide donor RR 0.89 [95% CI 0.34 to 2.33], 1 RCT, n=61 LOW quality evidence 8) Combined oral + vaginal misoprostol vs Vaginal misoprostol alone RR 1.81 (95% CI 0.60 to 5.50), 1 RCT, n=55 LOW quality evidence 9) Combined oral + vaginal misoprostol vs Oral misoprostol alone RR 0.47 (95% CI 0.23 to 0.96), 1 RCT, n=56 MODERATE quality evidence 10) Sublingual misoprostol vs Vaginal misoprostol RR 0.24 (95% CI 0.08 to 0.74), 2 RCTs, n=202 LOW quality evidence 11) Sublingual misoprostol vs Oral misoprostol RR 0.22 (95% CI 0.01 to 4.99), 2 RCTs, n=204 VERY LOW quality evidence 12) Low dose vaginal misoprostol (< 800 mcg) vs Moderate dose vaginal misoprostol (800 mcg to 2400 mcg) RR 1.85 (95% CI 1.13 to 3.03), 1 RCTs, n=150 LOW quality evidence	administration, with particular attention to standardised reporting of all relevant outcomes and assessment of rare adverse events. Further information is required about the use of sublingual misoprostol in this setting.
Medical treatment for early fetal death	14	1248	**Population: Pregnant women with early fetal death (<24 weeks gestation)**	Medical treatment with vaginal

(less than 24 weeks) Lemmers 2019 Cochrane			<u>Outcome: Complete miscarriage</u> 1) Vaginal misoprostol vs Placebo RR 4.23 (95% CI 3.01 to 5.94), 5 RCTs, n=305 LOW quality evidence 2) Vaginal misoprostol vs Surgical evacuation of uterus RR 0.40 (95% CI 0.32 to 0.50), 9 RCTs, n=943 LOW quality evidence All comparisons below were LOW or VERY LOW-quality evidence 3) Vaginal misoprostol vs Expectant management RR 1.25 (95% CI 1.09 to 1.45), 1 RCT, n=614 4) Vaginal misoprostol vs Vaginal dinoprostone RR 1.83 (95% CI 1.37 to 2.46), 2 RCTs, n=125 5) Vaginal misoprostol lower dose vs Vaginal misoprostol higher dose RR 0.82 (95% CI 0.58 to 1.14), 2 RCTs, n=397 6) Vaginal misoprostol wet vs Vaginal misoprostol dry RR 1.00 (95% CI 0.90 to 1.12), 1 RCT, n=320 7) Vaginal misoprostol + Methotrexate vs Vaginal misoprostol RR 1.13 (95% CI 0.85 to 1.50), 1 RCT, n=21 8) Vaginal misoprostol + Laminaria vs Vaginal misoprostol RR 1.83 (95% CI 1.37 to 2.46), 2 RCTs, n=125	misoprostol may be an acceptable alternative to surgical evacuation or expectant management. Further research is necessary to assess the effectiveness, safety and side effects, optimal route of administration and dose of different medical treatments for early fetal death.

			9) Vaginal misoprostol vs Sublingual misoprostol RR 0.84 (95% CI 0.61 to 1.16), 5 RCTs, n=513 10) Vaginal misoprostol vs Intravenous oxytocin RR 1.10 (95% CI 0.96 to 1.25), 1 RCT, n=85 11) Vaginal misoprostol vs Vaginal gemeprost RR 1.24 (95% CI 0.90 to 1.70), 1 RCT, n=50 12) Sublingual misoprostol vs Oral misoprostol RR 1.07 (95% CI 0.88 to 1.30), 2 RCTs, n=238 13) Sublingual powdery misoprostol vs Sublingual compact misoprostol RR 0.96 (95% CI 0.66 to 1.41), 1 RCT, n=54 14) Sublingual extended course misoprostol vs Sublingual non-extended course misoprostol RR 1.01 (95% CI 0.93 to 1.10), 1 RCT, n=180 15) Sublingual + vaginal misoprostol vs Vaginal misoprostol RR 1.00 (95% CI 0.85 to 1.18), 1 RCT, n=80 16) Oral misoprostol vs Vaginal misoprostol RR 0.68 (95% CI 0.45 to 1.03), 4 RCTs, n=418 17) Oral misoprostol + Mifepristone vs Expectant management RR 1.08 (95% CI 0.90 to 1.30), 1 RCT, n=122	

			18) Buccal misoprostol lower dose regimen vs Buccal misoprostol higher dose regimen RR 0.71 (95% CI 0.58 to 0.86), 1 RCT, n=270 19) Mifepristone + Vaginal misoprostol vs Vaginal misoprostol RR 1.18 (95% CI 0.95 to 1.47), 3 RCTs, n=447 20) Vaginal gemeprost vs Surgical evacuation of uterus RR 0.80 (95% CI 0.67 to 0.96), 1 RCT, n=87 21) Misoprostol intravaginal extra-amniotic vs Vaginal misoprostol RR 1.10 (95% CI 1.00 to 1.22), 1 RCT, n=180 22) Vaginal misoprostol (extended course) vs Vaginal misoprostol (non-extended course) RR 1.00 (95% CI 0.92 to 1.09), 2 RCTs, n=351	
Incomplete miscarriage management				
Medical treatments for incomplete miscarriage Kim 2017 Cochrane	17	4012	**Population: Women with incomplete miscarriage** <u>Outcome: Complete miscarriage</u> 1) Misoprostol vs Expectant care RR 1.23 (95% CI 0.72 to 2.10), 2 RCTs, n=150 VERY LOW quality evidence 2) Misoprostol vs Surgery RR 0.96 (95% CI 0.94 to 0.98), 15 RCTs, n=3862 VERY LOW quality evidence 3) Vaginal misoprostol vs Expectant care	Medical treatment, with misoprostol, and expectant care are both acceptable alternatives to routine surgical evacuation. Long-term follow-up studies are needed to

			RR 1.23 (95% CI 0.72 to 2.10), 2 RCTs, n=150 VERY LOW quality evidence 4) Vaginal misoprostol vs Surgery RR 0.89 (95% CI 0.84 to 0.95), 5 RCTs, n=364, VERY LOW quality evidence 5) Oral misoprostol vs Surgery RR 0.98 (95% CI 0.95 to 1.00), 7 RCTs, n=1884 LOW quality evidence All comparisons below are VERY LOW-quality evidence 6) Vaginal + oral misoprostol vs Surgery RR 0.95 (95% CI 0.87 to 1.04), 1 RCT, n=80, 7) Sublingual misoprostol vs Surgery RR 0.96 (95% CI 0.95 to 0.98), 2 RCTs, n=1534 8) Vaginal misoprostol vs Oral Misoprostol RR 0.94 (95% CI 0.76 to 1.16), 1 RCT, n=198 9) Oral misoprostol 600mcg vs Oral Misoprostol 1200mcg RR 1.00 (95% CI 0.93 to 1.07), 2 RCTs, n=464 10) Oral mifepristone + Vaginal misoprostol vs Surgery RR 1.00 (95% CI 0.78 to 1.27), 1 RCT, n=16 11) Sublingual misoprostol vs Oral misoprostol RR 0.99 (95% CI 0.94 to 1.05), 2 RCTs, n=358	confirm these findings. There is an urgent need for studies on women who miscarry at more than 13 weeks' gestation.

Surgical procedures to evacuate incomplete miscarriage Tunçalp 2010 Cochrane	2	463	**Population: Pregnant women with incomplete miscarriage, regardless of the cause of the incomplete miscarriage** <u>Intervention & Comparator: Vacuum aspiration vs Sharp metal curettage</u> 1) Uterine perforation RR 0.32 (95% CI 0.01 to 7.76), 2 RCTs, n=448 LOW quality evidence 2) Need for re-evacuation RR 1.50 (95% CI 0.29 to 7.83), 2 RCTs, n=463 VERY LOW quality evidence 3) Duration of procedure Vacuum aspiration was associated with shorter duration MD -1.20 minutes (95% CI -1.53 to -0.87 minutes), 1 RCT, n=357 LOW quality evidence 4) Post-abortal infection/sepsis RR 0.27 (95% CI 0.06 to 1.29), 1 RCT, n=270 LOW quality evidence 5) Blood loss Vacuum aspiration was associated with decreased blood loss MD -17.10 ml (95% CI -24.05 to -10.15 ml), 1 RCT, n=357 LOW quality evidence	Vacuum aspiration is safe, quick to perform, and less painful than sharp curettage. Different sources of vacuum pressure, cannula types, methods of analgesia, and duration of hospital stay have not been evaluated and should be researched further.
Other miscarriage related complications management				

Antibiotics for incomplete abortion May 2007 Cochrane	1	135	**Population: Women with incomplete miscarriage (bleeding or pain or passing products of conception). Women with signs and symptoms of infection were not included. No gestational age limit was imposed.** <u>Outcome: Post-abortal sepsis</u> 1) Tetracycline capsules (500mg four times a day for one week) + evacuation of uterus vs Evacuation of uterus RR 1.61 (95% CI 0.79 to 3.26), 1 RCT, n=135 LOW quality evidence	There is not enough evidence to evaluate a policy of routine antibiotic prophylaxis to women with incomplete abortion.
Antibiotics for treating septic abortion Udoh 2016 Cochrane	3	233	**Population: Women with a septic miscarriage** <u>Outcome: Reduction in fever in all women</u> 1) Clindamycin vs Penicillin + Chloramphenicol MD -12.30 (95% CI -25.12 to 0.52), 1 RCT, n=77 MODERATE quality evidence. <u>Outcome: Time to fever resolution (mean time)</u> 1) Penicillin + Chloramphenicol vs Cephalothin + Kanamycin MD -2.30 (95% CI -17.31 to 12.71), 1 RCT, n=56 LOW quality evidence <u>Outcome: Fever resolution time (mean days)</u> 1) Tetracycline vs Penicillin G MD -5.03 (95% CI -5.77, -4.29), 1 RCT, n=100 LOW quality evidence	There is no strong evidence that intravenous clindamycin alone was better than penicillin plus chloramphenicol for treating women with septic abortion There is a need for high-quality RCTs providing reliable evidence for treatments of septic abortion

				with antibiotics that are currently in use.

Table 19: Outcomes from included systematic reviews looking at the management of miscarriage

Discussion

Main findings

With regard to interventions for prevention of miscarriage in asymptomatic women, the majority of the meta-analyses presented did not find any benefit for the use of the interventions studied for either miscarriage or live-birth. For immunotherapy-based interventions, only prednisolone was shown to have some benefit for both miscarriage and live-birth compared to placebo in women with unexplained RM. No benefits were shown for anticoagulant or antiplatelet interventions and aspirin maybe harmful for women with RM and APS. Progesterone was shown to be beneficial in reducing miscarriage in women with RM but oestrogen was not. Thyroxine may be beneficial in women with subclinical hypothyroidism and women with thyroid autoimmunity but no other endocrine system-based interventions were shown to be beneficial. Metformin may be beneficial for women with PCOS and subfertility but the evidence is not consistent. The benefits of cervical cerclage in women at high risk of miscarriage remain unproven. There was no evidence for hysteroscopic resection of septa in septate uteri. There was insufficient evidence of any benefit for endometrial injury, bed rest or any micronutrient combinations. There was a possible benefit of Chinese herbal medicines, particularly with progesterone, but again this evidence was not of high-quality.

For interventions for the prevention of miscarriage in symptomatic women, there was significantly less evidence in total. There was evidence of benefit for the use of progesterone in women with a threatened miscarriage and of CHM in combination with western medicines. For the management of first trimester miscarriage, surgical management was shown to be

better than expectant management but this was not the same for second trimester miscarriage.

There is a large volume of systematic review level evidence that exists around the prevention of miscarriage in various patient populations, treating threatened miscarriage and managing a miscarriage. Yet very little of this evidence is of high or even moderate quality. Systematic reviews of randomised controlled trials are the highest level of evidence (222) which policymakers and guideline groups seek or create during the development of guidelines, and are therefore the basis of the evidence-based medicine which clinicians' practice. Therefore, we must be aware that many of the practices and treatments clinicians use are not based on high-quality evidence and it is essential that patients are counselled as such.

Strengths and weaknesses

A key strength of this chapter is the through search strategy, developed with the assistance of a women's health information scientist. A further strength lies in the use of a recognised systematic review filter to narrow the search to only systematic reviews, ensuring that the search was intentional and direct. The entire study selection, quality assessment and data extraction process was carried out independently, by two reviewers to minimise the risk of bias and errors during the entire review process. We recognise that our search strategy did not search an extensive list of databases, however limiting it to PubMed and Cochrane alone was felt to be thorough enough to obtain all the systematic reviews we aimed to capture. We also recognise that our search strategy was not designed to capture unpublished reviews,

governmental reviews or industry reviews. We were not able to perform a quality assessment of all the comparisons and outcomes as we were limited by the information that the original review authors presented in their reviews. We understand that it was often the rules stipulated by the publishing journals that may have limited the amount of information in the main review or supplementary information that reviewers could provide. To the best of our knowledge this is the first work that amalgamates all the highest-quality evidence available surrounding miscarriage.

Interpretation

Clinicians providing care to women with miscarriages and recurrent miscarriage need to be aware that whilst they maybe basing their clinical decisions on the best available evidence and guidelines, that this evidence is often not of high or even moderate-quality and this should be highlighted during consultations with individual patients. Guideline development groups worldwide, should be clear when producing advice that clinicians should base their treatment decisions in the context of the quality of the evidence by which it is underpinned, and be conscious of not overstating any potential benefits.

This work highlights the need for a significant amount of further, adequately-powered, high-quality, randomised research is required to provide additional results for meta-analysis in the majority of the areas examined by this review. Future research efforts worldwide, need to take a more coordinated and directed view to produce this research, with the help of funding

bodies and in conjunction with large organisations such as the RCOG, ACOG, ESHRE, FIGO and WHO, who should allocate limited resources to targeted areas to avoid duplication of effort.

Conclusion

Women and couples should be adequately counselled regarding the lack of high-quality evidence for many interventions for the management of miscarriage and recurrent miscarriage. Further high-quality randomised trial evidence is required for many interventions to inform and improve the quality of recommendations surrounding the management of miscarriage and recurrent miscarriage.

CHAPTER SIX:

THESIS CONCLUSIONS

i) Introduction

This body of work has attempted to further the knowledge and evidence base surrounding miscarriage in order to improve the management of women who suffer from a miscarriage. Using three different evidence synthesis methods and performing primary research in the form of a prospective cohort study, this thesis has sought to answer the following questions, originally laid out in chapter one.

A. What is the association between hydrosalpinx and miscarriage?
B. What is the effect of treatment for hydrosalpinx on miscarriage?
C. What is the prevalence of blocked tubes and hydrosalpinx in the recurrent miscarriage population?
D. What is the prognosis of women with blocked tubes or a hydrosalpinx who are trying for a pregnancy?
E. What is the best method of managing a miscarriage?
F. What is the current body of evidence surrounding the management of miscarriage?

In this final chapter, the findings of this thesis will be discussed in relation to the original questions that were posed above. The potential impact on clinical management, public policy and future research will also be discussed.

ii) What is the association between hydrosalpinx and miscarriage?

This question was primarily answered by the systematic review and meta-analysis of 14 observational studies presented in chapter two. A 74% increase in the risk of miscarriage was

noted during meta-analysis in women with a hydrosalpinx. Interestingly, a 136% increase in the risk of miscarriage at the biochemical stage of pregnancy, was found. However, no significant difference was found in the risk of a clinical pregnancy loss. It appears, therefore that there is an association between hydrosalpinx and miscarriage and that hydrosalpinx increases the risk of miscarriage. The risk is highest in the early stages of a pregnancy, before it is visible on ultrasound and can be considered a clinical pregnancy. It has been well established that hydrosalpinx has a negative impact on pregnancy outcomes in the IVF population and this is due to low implantation rates (105,115). Potentially increased miscarriage rates had previously been noted by researchers (126,132) and this systematic review and meta-analysis agrees with and confirms the evidence, that hydrosalpinx continues to pose a threat to a developing pregnancy after implantation and increases the risk of pregnancy loss albeit mainly in the IVF population. Fallopian tube disease and hydrosalpinx as a risk factor for miscarriage is not discussed in either the RCOG Green top guideline on the investigation and treatment of couples with recurrent miscarriage, or in the ESHRE guideline on the management of recurrent pregnancy loss or in the ACOG Practice bulletin on management of recurrent early pregnancy loss (5,7,9).

Whilst there are limitations, such as the studies on which this meta-analysis was based were of variable quality, the number of women in the hydrosalpinx cohort was small and the studies had some clinical heterogeneity in terms of their conduct. The strengths of the study such as, robust methodology, duplication of study selection and data extraction, extensive literature searches with advice from an information scientist and importantly, no severe statistical

heterogeneity, allow us to confidently state there is a clear signal of association from this work. Future research should aim to establish if the results presented are replicated in the natural conception population and the reasons why hydrosalpinges negatively impact both implantation and miscarriage. It should also aim to establish whether different aetiologies behind tubal damage affect pregnancy in different ways which could in turn help to discern treatment avenues with potential, so there are alternatives to IVF. Clinicians working in early pregnancy and fertility should be aware of this negative association and be counselling women and couples of the potential increase in the risk of miscarriage and in particular biochemical pregnancy loss with a hydrosalpinx both in assisted and natural conception. Clinical guidelines from specialist groups such as the RCOG, ESHRE and ACOG should also be updated to reflect this new data to help in the dissemination of this evidence.

iii) What is the effect of treatment for hydrosalpinx on miscarriage?

This question was also primarily answered by the systematic review presented in chapter two. However, it was the meta-analysis of seven randomised trials and six observational cohort studies that examined the effect of treatment. We found three categories of treatment for a hydrosalpinx which were ultrasound guided aspiration, tubal conservational surgery and salpingectomy-based surgery. Overall, treatment for hydrosalpinx appeared to reduce the risk of miscarriage by over half (54%). Reassuringly, this was consistent across both randomised and observational studies with no statistical heterogeneity. When each method of treatment for hydrosalpinx was explored separately, both women treated with tubal conservational surgery and women treated with salpingectomy-based surgery, again had less than half the risk of a miscarriage compared to women with an untreated hydrosalpinx (61% less and 56%

less respectively). This improvement of pregnancy outcomes is consistent, with the evidence for salpingectomy for women with hydrosalpinx prior to IVF (223), which has long been recommended by NICE (96). This was not the case for women treated with ultrasound guided aspiration for their hydrosalpinx, where no difference was detected between the groups. We can state therefore, that treatment of a hydrosalpinx using tubal-conservational surgery or salpingectomy-based surgery, appears to reduce the risk of a subsequent miscarriage in women undergoing IVF.

Whilst the total study population of the meta-analysis and the contribution of evidence from high-quality randomised trials were both small, the lack of statistical heterogeneity and consistency of the results again gives a clear signal of positive benefit, for the treatment of hydrosalpinx to reduce the risk of miscarriage in women undergoing IVF. If it is established that hydrosalpinx also increases the risk of miscarriage in natural conceptions then an adequately powered, definitive randomised trial is needed to confirm these findings are applicable to this population and to establish the best method for treatment of a hydrosalpinx, however, this may be difficult to conduct due to the widespread availability of IVF. Observational data shows us that tubal conservational techniques may well have a role in the treatment for hydrosalpinx but randomised data is still needed for clinicians to change practice confidently (224). As shown by the ESEP study on tubal pregnancy by Mol 2014 and a subsequent meta-analysis by Cheng 2016, it may well be that there is no significant difference for pregnancy outcomes between tubal-conservational surgery versus salpingectomy but this would be important to establish (225,226) especially for women with bilateral diseased tubes

who do not have access to IVF. Policy makers should include the best method for treating a hydrosalpinx as a research priority and funding bodies should direct research funding to investigate this. Whilst we wait for high-quality evidence, clinicians should cautiously counsel women and couples about the potential benefits of treatment for hydrosalpinx should they present with recurrent miscarriage and nil other causes found in the context of evidence presented.

iv) What is the prevalence of blocked tubes or a hydrosalpinx in the recurrent miscarriage population?

This question was primarily answered by the observational cohort study presented in chapter three. We found that out of 79 women who completed a HyCoSy scan, 29 had at least one blocked tube giving a prevalence of 36.7% (95% CI 26.1% to 48.3%) of any type of blocked tubes in the recurrent miscarriage population. Out of 81 women who attended for a HyCoSy scan, five had the sonographic appearances of a hydrosalpinx giving a prevalence of 6.2% (95% CI 2.0% to 18.8%) for hydrosalpinx in the recurrent miscarriage population. Blocked tubes are therefore a common problem in the recurrent miscarriage population. And as logically expected, hydrosalpinx, whilst not as prevalent as it is in the subfertile population (around 19% to 29%) (119), is prevalent in the recurrent miscarriage population in about 6% of women.

As discussed earlier in this chapter in section ii, tubal testing is not recommended during the investigation of women and couples with recurrent miscarriage. It is well established that hydrosalpinx has a negative affect for women undergoing IVF in terms of their pregnancy rates

(105,115). We have seen in the evidence from chapter two that hydrosalpinx specifically, also has a negative affect for miscarriage rates with a significantly increased risk of pregnancy loss especially during the biochemical phase of pregnancy. And now we have evidence that blocked fallopian tubes, which is how hydrosalpinges start to develop (227), are very common in the recurrent miscarriage population.

As this was a small study with some difficulties experienced during its conduct and some weaknesses in its methodology resulting in some results with wide confidence intervals, higher quality evidence is probably needed before national recommendations are made. Future research should aim to confirm the initial findings from this study as I believe this study provides the justification for further investigation of the prevalence of tubal disease in the recurrent miscarriage population. Tubal testing could, however, be continued to be offered in a research setting or perhaps as a second line investigation for all women being investigated for recurrent pregnancy loss, in whom routine investigations were negative. This should be investigated before national guidelines are changed.

v) <u>What is the prognosis of women with blocked tubes or a hydrosalpinx who are trying for a pregnancy?</u>

This question was also primarily answered by the observational cohort study presented in chapter three. Women with at least one blocked tube had lower pregnancy rates compared to women with patent tubes (RR 0.68; 95% CI 0.44, 1.00, p=0.03). Women with at least one blocked tube, were more than 100% more likely to suffer from a pregnancy loss at less than

or equal to 14 weeks gestation, in their first pregnancy after their HyCoSy, compared to women with patent tubes (RR 2.01; 95% CI 1.08, 3.72, p=0.05). Women with at least one blocked tube, were also less likely to have a live birth at greater than or equal to 24 weeks gestation, in their first pregnancy after their HyCoSy, compared to women with patent tubes (RR 0.38; 95% CI 0.13,1.07, p=0.04). Due to the small number of hydrosalpinges found, we cannot draw conclusions from this study regarding the prognosis of women with recurrent miscarriage and concurrent hydrosalpinx. We can, however, say that blocked tubes, have a negative impact on the key reproductive outcomes of pregnancy rates, miscarriage rates and live-birth rates which is in keeping with previous literature and the results of chapter two regarding hydrosalpinx in the IVF population.

The above, in conjunction with the evidence from chapter two discussed in sections ii and iii and the prevalence data discussed in section iv of this chapter allow us conclude the following. Hydrosalpinx is associated with higher pregnancy loss rates in the IVF population. Hydrosalpinx and tubal pathology are not specifically screened for during routine investigation for recurrent pregnancy loss. Whilst hydrosalpinx itself only appears to have a prevalence of around six percent in this population, blocked fallopian tubes, which are a precursor to hydrosalpinx (227), are seen in more than a third of these women. For women with blocked fallopian tubes on a HyCoSy, there appears to be an association with lower pregnancy rates, higher miscarriage rates and lower live-birth rates. Therefore, clinicians investigating this population should consider tubal testing particularly if other routine investigations are negative. If blocked tubes are found, clinicians should cautiously counsel women about the

potential negative impact of this, for their reproductive outcomes. Further research is needed to fully establish the extent of this problem in the recurrent miscarriage population and the feasibility of implementing this investigative pathway. If tubal pathology is established to be a significant problem in the recurrent miscarriage population then research efforts should be directed to establishing the best method of treatment for these women as this is unclear. Professional bodies and national guideline developers should consider incorporating this evidence into guidance to increase awareness of tubal pathology being associated with poorer reproductive outcomes. Despite the observational nature of this study, along with the relatively small population sampled, high drop-out rate and some statistically non-significant results, there is a clear signal which should be further researched and considered when investigating, counselling and treating women with recurrent pregnancy loss.

vi) What is the best method of managing a miscarriage?

This question was answered by the systematic review and network meta-analysis presented in chapter four. Miscarriage is a common problem and it has long been argued which of the available methods, all of whom are used commonly around the world, is the most appropriate first line treatment option (10). Network meta-analysis has globally become accepted as the basis for evidence for guidelines, initially through its use by national health technology assessment bodies and more recently by the WHO and Cochrane (228). It has many advantages over traditional meta-analysis as it allowed quantitative comparisons between multiple interventions for the same condition that may not have been directly compared in available trials. In addition, the combination of direct and indirect evidence can often increase

the certainty of the evidence, meaning subsequent guidance and recommendations are stronger and clinicians can feel more confident when applying them (228).

This network meta-analysis showed that purely in terms of completing a miscarriage, suction curettage with cervical preparation is the best method of treating a miscarriage (SUCRA 98.2%) and expectant management is the worst (0.0%). Surgical methods for completing a miscarriage are better than medical methods which in turn are better than expectant management. It also showed that for women with a missed miscarriage, the addition of mifepristone to misoprostol maybe advantageous. However, what is the best method of treating a miscarriage is not a judgement to be made purely on efficacy. Safety and side effects must also be considered. Expectant management was the lowest ranked method for serious complications (SUCRA 10.9%) and the second lowest for need for subsequent emergency surgery (SUCRA 26.6%). Medical methods were ranked bottom for side effects such as diarrhoea and vomiting. In addition to the above, women's views must also be considered, however, there was a lack of enough homogenous data from the included studies but overall, all methods were considered acceptable and had high satisfaction. To state what is the best method of treating a miscarriage and therefore should be recommended as first-line treatments in guidelines, is difficult to do and this network met-analysis does not do this entirely. We must consider all the outcomes presented in this network meta-analysis and further research work on other factors which may be considered important by women, such as future pregnancy outcomes or return to normal menstruation is needed. As such, a formal core-outcome set established via a robust and extensive Delphi process is needed.

Subsequently, evidence synthesis based on this core-outcome set would be needed for outcomes not investigated by this network meta-analysis. NICE should consequently incorporate this into a patient-centred comprehensive up to current guidance. However, what is clear, is that expectant management is the least efficacious method and probably has the highest risk of serious complications and emergency surgery. This should be communicated clearly to women being counselled about management of their miscarriage.

Reassuringly, the results from this network meta-analysis are in agreement with the four previous Cochrane reviews on similar topics, which adds to the certainty over the findings (210,217–219). Current NICE guidance is to offer expectant management as first-line treatment for the first seven to 14 days for women with a confirmed miscarriage unless there are clinical reasons why they should have medical or surgical treatment (43). Clinicians should now be fully counselling women that whilst all methods are broadly satisfactory for women, expectant management is likely to give them the least chance of completing a miscarriage with the highest risk of serious complications and higher risk of emergency surgery. However, other treatment options such as surgery and medical management do carry higher risks of side effects, infection and greater blood loss. Clinicians should also strongly consider the use of mifepristone in women with a missed miscarriage. Whilst not included in this network meta-analysis as it was recently published, Chu 2020, provided further evidence in the form of a large, methodologically robust, placebo-controlled trial, that mifepristone should be considered for women with a missed miscarriage (229).

Producers of clinical guidance should also consider updating their recommendations to reflect the findings of this network meta-analysis and consider removing expectant management as their first-line recommendation and recommending mifepristone for women with a missed miscarriage. Future research should focus on establishing all important factors women consider when deciding on their treatment to see if other factors not investigated by this network meta-analysis exist as well as the financial and service delivery costs of changing recommendations for treatment surrounding such a common complication of early pregnancy.

vii) What is the current body of evidence surrounding the management of miscarriage?

This question was answered by the narrative systematic overview review presented in chapter five. We categorised the available evidence into three areas: 1) interventions which could reduce miscarriage in women who were asymptomatic of the symptoms of miscarriage, 2) interventions which could reduce miscarriage in women who were symptomatic of the symptoms of miscarriage and 3) women who had already suffered from a miscarriage and needed treatment for a miscarriage. We included a total of 50 systematic reviews of randomised trials, 32, five and 13 systematic reviews in each of the above three categories respectively.

The majority of interventions for asymptomatic women were not shown to be effective at reducing miscarriage. Only prednisolone in women with idiopathic recurrent pregnancy loss,

progesterone in women with recurrent miscarriage, thyroxine in women with subclinical hypothyroidism and women with thyroid autoimmunity and metformin in women with PCOS and subfertility had a positive effect on miscarriage and or live-birth. Of particular note was that placebo ranked higher than aspirin alone for women with two or more miscarriages of unknown cause with or without thrombophilia and also higher than low molecular weight heparin plus aspirin for women with two or more miscarriages and antiphospholipid syndrome in one network meta-analysis (177). Importantly, the majority of evidence whether benefits were shown or where no difference was shown, was not of a high-quality, with low numbers of trials and participants, significant heterogeneity, wide confidence intervals and based on high or moderate risk of bias trials.

For women who were symptomatic, again there was evidence of benefit for progesterone but very little else. One comparison was even of high quality but the rest was moderate to low. And the majority of comparisons were based on low numbers of trials and participants or had significant heterogeneity or were not completely based on low risk of bias trials.

And finally, for women who had already suffered a miscarriage and required treatment, we found that for women with a first trimester miscarriage, expectant management is the least efficacious management option with the highest risk of serious complications. And for second trimester miscarriage, misoprostol may be an acceptable alternative to expectant management or surgical evacuation especially given sublingually. However, similar issues with quality remain. The majority of evidence was of very-low to moderate quality, it was based on

small numbers of trials and participants, the trials were of variable risk of bias often with significant heterogeneity.

Future research efforts should use newer methodologies for evidence synthesis such as network meta-analysis to establish rankings across a range of clinically important outcomes for second-trimester miscarriage as has been performed for earlier gestation pregnancy loss. Where it has been identified that good quality or any primary evidence is lacking, research funding bodies should direct efforts to remedy this. For example, primary research is needed for septum resection in women with a septate uterus. Guideline development groups from relevant organisations should incorporate the newer evidence and change recommendations, for example, no longer recommending expectant management as a first-line treatment option for first-trimester miscarriage or provide clinicians additional information to aid their counselling of women and couples. Clinicians should also aware of how little, and often of how low-quality, the evidence is for interventions to reduce miscarriage or improving live-birth and they should be cautious when counselling patients over their effectiveness so as not to overstate their benefits, especially considering the extra financial cost of some of these interventions. Empirical use of aspirin for recurrent miscarriage should be discontinued. It is also questionable whether many of these interventions should be used outside of a research setting, for example all immunotherapy interventions aside from prednisolone and endometrial injury are lacking evidence of benefit. Therefore, for interventions to reduce miscarriage, high-quality, randomised, adequately powered evidence is needed for the

majority of interventions to provide better quality evidence and justification for their use which is clearly lacking currently in the majority of cases.

viii) Summary of findings of thesis

Table 20: Summary of findings of thesis and structured questions and answers for each chapter of this thesis

Chapter Number	Population	Intervention	Comparison	Outcome(s)	Research Design
A. What is the association between hydrosalpinx and miscarriage?					
2	Women with an established pregnancy and a concurrent hydrosalpinx	NA	Women with an established pregnancy and no concurrent hydrosalpinx	• Miscarriage • Biochemical pregnancy loss • Clinical pregnancy loss • Ectopic Pregnancy	Systematic review and meta-analysis of observational studies
Summary of findings: • Hydrosalpinx increases the risk of miscarriage • This risk is highest early on in a pregnancy in the biochemical phase before it is visible on ultrasound.					
B. What is the effect of treatment for hydrosalpinx on miscarriage?					
2	Women with an established pregnancy and a concurrent hydrosalpinx	Treatment for a hydrosalpinx	No treatment for hydrosalpinx	• Miscarriage • Biochemical pregnancy loss • Clinical pregnancy loss • Ectopic Pregnancy	Systematic review and meta-analysis of observational studies and randomised trials
Summary of findings:					

- Treatment for hydrosalpinx appears to reduce the risk of miscarriage by approximately half.
- Tubal conservational surgery and salpingectomy-based surgery for the treatment of hydrosalpinx, appear to be better than ultrasound guided aspiration, for reducing the risk of miscarriage.

C. What is the prevalence of blocked tubes or hydrosalpinx in the recurrent miscarriage population?

3	Women with recurrent miscarriage	NA		• Presence of tubal blockage • Presence of hydrosalpinx • 7 secondary outcomes	Primary observational cohort study

Summary of findings:

- The prevalence of any type of blocked fallopian tubes in the recurrent miscarriage population is 36.7%.
- The prevalence of hydrosalpinx in the recurrent miscarriage population is 6.2%.

D. What is the prognosis of women with blocked tubes or hydrosalpinx who are trying for a pregnancy?

3	Women with recurrent miscarriage and concurrent blocked tubes or hydrosalpinx	NA	Women with recurrent miscarriage and no concurrent blocked tubes or hydrosalpinx	• Pregnancy • Miscarriage • Live birth • 4 secondary outcomes	Primary observational cohort study

Summary of findings:

- Women with blocked tubes have an over 30% lower pregnancy rate than women with patent tubes.

- Women with blocked tubes are more than twice as likely to have a pregnancy loss compared to women with patent tubes.
- Women with blocked tubes are less than half as likely to have a live birth beyond 24 weeks of than women with patent tubes.

E. What is the best method of managing a miscarriage?

4	Women having treatment for a miscarriage	• Expectant/ Placebo • Dilatation and curettage • Suction curettage • Suction curettage with cervical preparation • Mifepristone + Misoprostol • Misoprostol	• Complete miscarriage • Composite outcome of death and serious complications • 16 secondary outcomes	Systematic review and network-meta-analysis of randomised trials

Summary of findings:

- Suction curettage with cervical preparation is the best method for completing a miscarriage.
- Expectant management is the lowest ranked method for completing a miscarriage.
- Surgical methods for completing a miscarriage are better than medical methods which in turn are better than expectant management.
- Expectant management has the highest risk of serious complications and amongst the high risk of needing emergency surgery
- Medical methods have the highest risk of vomiting, diarrhoea and pyrexia.
- For women with a missed miscarriage, the addition of mifepristone to misoprostol maybe advantageous

F. What is the current body of evidence surrounding the management of miscarriage?

5	Women pregnant with a singleton pregnancy or women trying to become pregnant	Any clinical, behavioural or health system intervention	Any alternative intervention or no intervention including placebo	• Any miscarriage outcome • Any live birth outcome	Narrative systematic overview review of systematic reviews of randomised trials
Summary of findings: • Very few interventions have evidence of benefit for reducing miscarriage in both women who are symptomatic and asymptomatic of symptoms of miscarriage • Majority of evidence for interventions being of benefit or where no difference was shown, is very-low to moderate quality and based on small numbers of trials and participants. • Progesterone appears to be of benefit in both for women who are symptomatic and asymptomatic of symptoms of miscarriage. • All interventions to complete a miscarriage appear to be effective but surgical methods appear to be more effective than medical methods, which in turn are more effective than expectant management.					

ix) Conclusion

Miscarriage and pregnancy loss is an all-too-common complication of early-pregnancy, suffered by too many women and couples, that has often had too little research, resulting in clinical practice which is often underpinned by low quality evidence and limited treatment options. The body of work presented in this thesis, using both primary research methods and

three different evidence synthesis methods, has provided new evidence surrounding a risk factor for miscarriage that is currently not routinely investigated for and has begun to build the evidence base surrounding treatment options as well as identifying the future work that is now necessary. This work has also provided new evidence surrounding the management of women who have already miscarried and therefore challenges the recommended practice of using expectant management as first line treatment for these women. And finally, this work has explored and laid bare, how little high-quality evidence exists for the use of all the interventions or practices that are used in this field with regard to improving pregnancy outcomes and therefore reducing miscarriage. The totality of this work is but a small contribution to the significant research which is desperately needed to help improve our care for this all-too-common complication, suffered by too many women and couples.

REFERENCES

1. Gray H. The Female Genital Organs. In: Lewis W, editor. Anatomy of the Human Body [Internet]. 20th ed. New York: Bartleby; 2000 [cited 2021 Jan 17]. Available from: https://www.bartleby.com/107/illus1161.html
2. UK Parliament. Abortion Act 1967. 87 United Kingdom: The National Archives; Oct 27, 1967.
3. Moscrop A. Miscarriage or abortion?' Understanding the medical language of pregnancy loss in britain; a historical perspective. BMJ Medical Humanities. 2013 Dec;39(2):98–104.
4. Beard RW, Mowbray JF, Pinker GD. Miscarriage or Abortion? The Lancet. 1985 Nov;326(8464).
5. Regan L, Backos M, Rai R. The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage Green-top Guideline No. 17. 2011.
6. Prager S, Dalton VK, Allen RH, ACOG Committee on Practice Bulletins-Gynaecology. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 200: Early Pregnancy Loss. 2018.
7. Bender-Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, et al. Recurrent Pregnancy Loss - ESHRE Clinical practice guideline. 2017 Nov.
8. Kolte AM, Bernardi LA, Christiansen OB, Quenby S, Farquharson RG, Goddijn M, et al. Terminology for pregnancy loss prior to viability: A consensus statement from the ESHRE early pregnancy special interest group. Vol. 30, Human Reproduction. Oxford University Press; 2015. p. 495–8.
9. ACOG Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin Number 24: Management of recurrent early pregnancy loss. Vol. 78, International Journal of Gynecology and Obstetrics. John Wiley and Sons Ltd; 2002. p. 179–90.
10. Jurkovic D, Overton C, Bender-Atik R. Diagnosis and management of first trimester miscarriage. Vol. 346, BMJ (Online). 2013.
11. Miscarriage Association. Background information - Miscarriage [Internet]. [cited 2021 Jan 17]. Available from: https://www.miscarriageassociation.org.uk/media-queries/background-information/
12. Tommy's. Pregnancy loss statistics. https://www.tommys.org/baby-loss-support/pregnancy-loss-statistics.
13. NHS Digital Secondary Care Analysis group. NHS Maternity Statistics, 2018-19 - Hospital Episode Statistics. 2019.

14. NHS Improvement. National Scedule of Reference Costs - Year 2018-19 - NHS trusts and NHS Foundation trusts [Internet]. 2019 [cited 2021 Jan 13]. Available from: https://www.england.nhs.uk/national-cost-collection/#ncc1819

15. Farren J, Mitchell-Jones N, Verbakel JY, Timmerman D, Jalmbrant M, Bourne T. The psychological impact of early pregnancy loss. Human Reproduction Update. 2018 Nov 1;24(6):731–49.

16. Williams HM, Topping A, Coomarasamy A, Jones LL. Men and Miscarriage: A Systematic Review and Thematic Synthesis. Qualitative Health Research. 2020 Jan 1;30(1):133–45.

17. Lok IH, Neugebauer R. Psychological morbidity following miscarriage. Best Practice and Research: Clinical Obstetrics and Gynaecology. 2007 Apr;21(2):229–47.

18. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. A Comparison of Medical Management with Misoprostol and Surgical Management for Early Pregnancy Failure. New England Journal of Medicine [Internet]. 2005;353(8):761–9. Available from: www.nejm.org

19. Macklon NS, Geraedts JPM, Fauser BCJM. Conception to ongoing pregnancy: the "black box" of early pregnancy loss. Human Reproduction Update. 2002;8(4):333–43.

20. Bai G, Korfage IJ, Hafkamp-De Groen E, Jaddoe VWV, Mautner E, Raat H. Associations between nausea, vomiting, fatigue and health-related quality of life of women in early pregnancy: The generation r study. PLoS ONE. 2016 Nov 1;11(11).

21. Jenkins A, Millar S, Robins J. Denial of pregnancy – a literature review and discussion of ethical and legal issues. Journal of the Royal Society of Medicine. 2011 Jul 3;104(7).

22. Olszynko-Gryn J. Reproduction: Antiquity to the Present Day. Hopwood N, Flemming R, Kassell L, editors. Cambridge University Press; 2018.

23. Lemmers M, Verschoor MAC, Hooker AB, Opmeer BC, Limpens J, Huirne JAF, et al. Dilatation and curettage increases the risk of subsequent preterm birth: A systematic review and meta-analysis. Human Reproduction. 2016 Jan 1;31(1):34–45.

24. Santamaria X, Isaacson K, Simón C. Asherman's Syndrome: It may not be all our fault. Human Reproduction. 2018;33(8):1374–80.

25. Coombes R. Obstetricians seek recognition for Chinese pioneers of safe abortion. BMJ. 2008 Jun 14;336(7657).

26. Kerslake D, Casey D. Abortion induced by means of the uterine aspirator. Obstet Gynecol. 1967 Jul;30(1):35–47.

27. Dingfelder J. Induced Abortion. In: Cibils L, editor. Surgical Diseases in Pregnancy. New York: Springer; 1990. p. 25–39.

28. Karman H, Potts M. Very early abortion using syringe as vacuum source. Lancet. 1972 May 13;1(7759):1051–2.

29. Siassakos D, Hamilton J, Newell S, Hollamby S. Surgical Management of Miscarriage and Removal of Persistent Placental or Fetal Remains: RCOG Consent Advice No. 10 (Joint with AEPU). London; 2018 Jan.

30. Amarin ZO, Badria LF. A survey of uterine perforation following dilatation and curettage or evacuation of retained products of conception. Archives of Gynecology and Obstetrics. 2005 Mar 24;271(3).

31. Deans R, Abbott J. Review of Intrauterine Adhesions. Journal of Minimally Invasive Gynecology. 2010 Sep;17(5).

32. Fritsch H. Ein Fall von volligen Schwund der Gebaumutterhohle nach Auskratzung. Zentralbl Gynaekol. 1894;18:1337–42.

33. Asherman JG. Traumatic intrauterine adhesions. J Obstet Gynaecol Br Emp. 1948;57:892–892.

34. Schenker JG, Margalioth EJ. Intrauterine adhesions: an updated appraisal. Vol. 37, Fertility and Sterility. 1982. p. 593–610.

35. Deans R, Vancaillie T, Ledger W, Liu J, Abbott JA. Live birth rate and obstetric complications following the hysteroscopic management of intrauterine adhesions including Asherman syndrome. Human Reproduction. 2018 Oct 1;33(10).

36. Santamaria X, Isaacson K, Simón C. Asherman's Syndrome: it may not be all our fault. Human Reproduction. 2018 Aug 1;33(8).

37. Smikle C, Yarrarapu S, Khetarpal S. Asherman Syndrome. In: StatPearls. Florida: Treasure Island; 2021.

38. Weeks A, Faúndes A. Misoprostol in obstetrics and gynecology. International Journal of Gynecology and Obstetrics. 2007;99(SUPPL. 2):S156–9.

39. The Editors of Encyclopaedia Britannica, editor. Mifepristone. In: Encyclopædia Britannica. Encyclopædia Britannica; 2017.

40. ACOG Committee on Obstetric Practice. New U.S. Food and Drug Administration Labeling on Cytotec (Misoprostol) Use and Pregnancy - ACOG Committee Opinion Number 283. Obstet Gynecol. 2003 May;101(5):1049–50.

41. World Health Organization Model List of Essential Medicines, 21st List, 2019. Geneva; 2019.

42. World Health Organisation Model List of Essential Medicines 14th edition (March 2005). Geneva; 2005 Mar.

43. Lumsden MA, Blake F, Davies N, Easton K, Faruharson R, Fletcher J, et al. NICE Clinical Guideline: Ectopic pregnancy and miscarriage: Diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. 2012.

44. Regan L, Rai R. Epidemiology and the medical causes of miscarriage. Bailliere's Best Practice and Research in Clinical Obstetrics and Gynaecology. 2000;14(5):839–54.

45. Goddijn M, Leschot NJ. Genetic aspects of miscarriage. Bailliere's Best Practice and Research in Clinical Obstetrics and Gynaecology. 2000;14(5):855–65.

46. Blomberg M, Birch Tyrberg R, Kjølhede P. Impact of maternal age on obstetric and neonatal outcome with emphasis on primiparous adolescents and older women: a Swedish Medical Birth Register Study. BMJ Open. 2014 Sep 24;4(e005840).

47. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: Population based register linkage study. British Medical Journal. 2000 Jun 24;320(7251):1708–12.

48. Li D-K, Odouli R, Wi S, Janevic T, Golditch I, Bracken TD, et al. A Population-Based Prospective Cohort Study of Personal Exposure to Magnetic Fields during Pregnancy and the Risk of Miscarriage. Epidemiology. 2002 Jan;13(1).

49. Harlap S, Shiono PH, Ramcharan S. Human Embryonic and Fetal Death. Porter IH, Hook EB, editors. New York: New York: Academic Press; 1980. 145–164.

50. Taylor WF. The probability of fetal death. Excepta Medica. 1970 Sep 7;307–20.

51. Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. Obstetrics and gynecology. 2004 Feb;103(2):219–24.

52. Ehrenberg HM, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. American Journal of Obstetrics and Gynecology. 2004 Sep;191(3):964–8.

53. Sebire NJ, Jolly M, Harris JP, Wadsworth J, Joffe M, Beard RW, et al. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. International Journal of Obesity [Internet]. 2001;25:1175–82. Available from: www.nature.com/ijo

54. Jungheim ES, Travieso JL, Carson KR, Moley KH. Obesity and Reproductive Function. Obstetrics and Gynecology Clinics of North America. 2012 Dec;39(4):479–93.

55. Wise LA, Rothman KJ, Mikkelsen EM, Sørensen HT, Riis A, Hatch EE. An internet-based prospective study of body size and time-to-pregnancy. Human Reproduction. 2010;25(1):253–64.

56. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: Matched case-control study. Human Reproduction. 2004;19(7):1644–6.

57. Sépaniak S, Forges T, Monnier-Barbarino P. Cigarette smoking and fertility in women and men. Gynécologie Obstétrique & Fertilité. 2006 Oct;34(10).

58. van Voorhis BJ, Dawson JD, Stovall DW, Sparks AET, Syrop CH. The Effects of Smoking on Ovarian Function and Fertility During Assisted Reproduction Cycles. Obstet Gynecol. 1996 Nov;88(5):785–91.

59. Yang HJ, Suh PS, Kim SJ, Lee SY. Effects of smoking on menopausal age: Results from the Korea national health and nutrition examination survey, 2007 to 2012. Journal of Preventive Medicine and Public Health. 2015 Jul 1;48(4):216–24.

60. Whitcomb BW, Purdue-Smithe AC, Szegda KL, Boutot ME, Hankinson SE, Manson JE, et al. Cigarette Smoking and Risk of Early Natural Menopause. American Journal of Epidemiology. 2018 Aug 10;187(4):696–704.

61. American Society for Reproductive Medicine. Smoking and inferility factsheet. ASRM. 2014;

62. Zhang BY, Wei YS, Niu JM, Li Y, Miao ZL, Wang ZN. Risk factors for unexplained recurrent spontaneous abortion in a population from southern China. International Journal of Gynecology and Obstetrics. 2010 Oct 13;108(2):135–8.

63. Winter E, Wang J, Davies MJ, Norman R. Early pregnancy loss following assisted reproductive technology treatment. Human Reproduction [Internet]. 2002;17(12):3220–3. Available from: https://academic.oup.com/humrep/article-abstract/17/12/3220/569615

64. Stefanidou EM, Caramellino L, Patriarca A, Menato G. Maternal caffeine consumption and sine causa recurrent miscarriage. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2011;158(2):220–4.

65. Greenwood DC, Alwan N, Boylan S, Cade JE, Charvill J, Chipps KC, et al. Caffeine intake during pregnancy, late miscarriage and stillbirth. European Journal of Epidemiology. 2010 Apr;25(4):275–80.

66. James JE. Maternal caffeine consumption and pregnancy outcomes: a narrative review with implications for advice to mothers and mothers-to-be. BMJ Evidence-Based Medicine. 2020 Aug 25;

67. Avalos LA, Roberts SCM, Kaskutas LA, Block G, Li DK. Volume and type of alcohol during early pregnancy and the risk of miscarriage. Substance Use and Misuse. 2014;49(11):1437–45.

68. Rai R-S, Clifford K, Cohen H, Regan L. High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. Human Reproduction. 1995;10(12):3301–4.

69. Miyakis S, Lockshin M, Atsumi T, Branch D, Brey R, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). Journal of Thrombosis and Haemostasis. 2006;4:295–306.

70. van den Boogaard E, Cohn DM, Korevaar JC, Dawood F, Vissenberg R, Middeldorp S, et al. Number and sequence of preceding miscarriages and maternal age for the prediction of antiphospholipid syndrome in women with recurrent miscarriage. Fertility and Sterility. 2013 Jan;99(1):188–92.

71. Kovalevsky G, Gracia CR, Berlin JA, Sammel MD, Barnhart KT. Evaluation of the Association Between Hereditary Thrombophilias and Recurrent Pregnancy Loss. Archives of Internal Medicine. 2004 Mar 8;164(5).

72. Bradley LA, Palomaki GE, Bienstock J, Varga E, Scott JA. Can Factor v Leiden and prothrombin G20210A testing in women with recurrent pregnancy loss result in improved pregnancy outcomes?: Results from a targeted evidence-based review. Genetics in Medicine. 2012 Jan;14(1):39–50.

73. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: A meta-analysis. Lancet. 2003 Mar 15;361(9361):901–8.

74. Parand A, Zolghadri J, Nezam M, Afrasiabi A, Haghpanah S, Karimi M. Inherited Thrombophilia and Recurrent Pregnancy Loss. Iranian Red Crescent Medical Journal. 2013 Dec 5;15(12).

75. Tal J, Schliamser LM, Leibovitz Z, Ohel G, Attias D. A possible role for activated protein C resistance in patients with first and second trimester pregnancy failure. Human Reproduction [Internet]. 1999;14(6):1624–7. Available from: http://humrep.oxfordjournals.org/

76. Hanson U, Persson B, Thunell S. Relationship between haemoglobin Aac in early Type 1 (insulin-dependent) diabetic pregnancy and the occurrence of spontaneous abortion and fetal malformation in Sweden. Diabetologia. 1990;33:100–4.

77. Zolghadri J, Tavana Z, Kazerooni T, Soveid M, Taghieh M. Relationship between abnormal glucose tolerance test and history of previous recurrent miscarriages, and beneficial effect of metformin in these patients: a prospective clinical study. Fertility and Sterility. 2008 Sep;90(3):727–30.

78. Mills J, Simpson J, Driscoll S, Jovanovic-Peterson L, van Allen M, Aarons J, et al. Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. New England Journal of Medicine. 1988 Dec 22;319(25):1617–23.

79. Taylor PN, Minassian C, Rehman A, Iqbal A, Draman MS, Hamilton W, et al. TSH levels and risk of miscarriage in women on long-term levothyroxine: A community-based study. Journal of Clinical Endocrinology and Metabolism. 2014 Oct 1;99(10):3895–902.

80. Schneuer FJ, Nassar N, Tasevski V, Morris JM, Roberts CL. Association and predictive accuracy of high TSH serum levels in first trimester and adverse pregnancy outcomes. Journal of Clinical Endocrinology and Metabolism. 2012 Sep;97(9):3115–22.

81. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid. 2002 Jan 1;12(1):63–8.

82. Giakoumelou S, Wheelhouse N, Cuschieri K, Entrican G, Howie SEM, Horne AW. The role of infection in miscarriage. Human Reproduction Update. 2016;22(1):116–33.

83. Chan YY, Jayaprakasan K, Zamora J, Thornton JG, Raine-Fenning N, Coomarasamy A. The prevalence of congenital uterine anomalies in unselected and high-risk populations: A systematic review. Human Reproduction Update. 2011 Nov;17(6):761–71.

84. Venetis CA, Papadopoulos SP, Campo R, Gordts S, Tarlatzis BC, Grimbizis GF. Clinical implications of congenital uterine anomalies: A meta-analysis of comparative studies. Reproductive BioMedicine Online. 2014 Dec 1;29(6):665–83.

85. The Editors of Encyclopaedia Britannica. Gabriel Fallopius. In: The Editors of Encyclopaedia Britannica, editor. Encyclopaedia Britannica [Internet]. Encyclopaedia Britannica; 2021 [cited 2021 Jan 14]. Available from: https://www.britannica.com/biography/Gabriel-Fallopius

86. The Editors of Encyclopaedia Britannica. Fallopian tube. In: The Editors of Encyclopaedia Britannica, editor. Encyclopædia Britannica [Internet]. Encyclopaedia Britannica; 2020 [cited 2021 Jan 14]. Available from: https://www.britannica.com/science/fallopian-tube

87. Public Health England. Sexually transmitted infections and screening for chlamydia in England, 2018 - Health Protection Report, Volume 13, Number 19. 2019 Jun.

88. Martin DH, Koutsky L, Eschenbach DA, Daling JR, Russell Alexander E, Benedetti JK, et al. Prematurity and Perinatal Mortality in Pregnancies Complicated by Maternal Chlamydia trachomatis Infections. Journal of the American Medical Association [Internet]. 1982;247(11):1585–8. Available from: http://jama.jamanetwork.com/

89. Gravett MG, Nelson ; H Preston, Derouen T, Critchlow C, Eschenbach DA, Holmes KK. Independent Associations of Bacterial Vaginosis and Chlamydia trachomatis Infection With Adverse Pregnancy Outcome. Journal of the American Medical Association [Internet]. 1986;256(14):1899–903. Available from: http://jama.jamanetwork.com/

90. Rowley J, Toskin I, Ndowa F. Global incidence and prevalence of selected curable sexually transmitted infections - 2008, WHO report. Geneva; 2012.

91. Haggerty CL, Gottlieb SL, Taylor BD, Low N, Xu F, Ness RB. Risk of sequelae after chlamydia trachomatis genital infection in women. Journal of Infectious Diseases. 2010 Jun 15;201(Supp 2):S134–55.

92. Stevens JS, Criss AK. Pathogenesis of Neisseria gonorrhoeae in the female reproductive tract: Neutrophilic host response, sustained infection, and clinical sequelae. Current Opinion in Hematology. 2018 Jan 1;25(1):13–21.

93. Khalaf Y. Tubal subfertility. BMJ. 2003 Sep 13;327(7415):610–3.

94. Cates W, Wasserheit JN. Genital chlamydial infections: Epidemiology and reproductive sequelae. American Journal of Obstetrics and Gynecology. 1991 Jun;164(6 PART 2):1771–81.

95. Zeyneloglu HB, Arici A, Olive DL. Adverse effects of hydrosalpinx on pregnancy rates after in vitro fertilization-embryo transfer. Fertility and Sterility. 1998 Sep;70(3):492–9.

96. Treasure T, Bewley S, Bhattacharya S, Brian K, Child T, Davies M, et al. NICE Clinical Guideline: Fertility: assessment and treatment for people with fertility problems [Internet]. 2013 Feb. Available from: www.cla.co.uk].

97. Eytan O, Azem F, Gull I, Wolman I, Elad D, Jaffa AJ. The mechanism of hydrosalpinx in embryo implantation. Human Reproduction. 2001 Dec;16(12).

98. Mansour RT, Aboulghar MA, Serour GI, Riad R. Fluid Accumulation of the Uterine Cavity Before Embryo Transfer: A Possible Hindrance for Implantation. Journal of in Vitro Fertilization and Embryo Transfer. 1991;8(3):157–9.

99. Sharara FI. What effect does hydrosalpinx have on assisted reproduction? The role of hydrosalpinx in IVF: simply mechanical? Human Reproduction [Internet]. 1999;14(3):577–8. Available from: http://humrep.oxfordjournals.org/

100. Lu S, Peng H, Zhang H, Zhang L, Cao Q, Li R, et al. Excessive Intrauterine Fluid Cause Aberrant Implantation and Pregnancy Outcome in Mice. PLoS ONE. 2013 Oct 23;8(10).

101. Mukherjee T, Copperman AB, McCaffrey C, Anne Cook C, Maria Bustillo M, Obasaju MF. Hydrosalpinx fluid has embryotoxic effects on murine embryogenesis: a case for prophylactic salpingectomy. Fertility and Sterility. 1996;66(5):851–3.

102. Cohen MA, Lindheim SR, Sauer M v. Hydrosalpinges adversely affect implantation in donor oocyte cycles*. Human Reproduction [Internet]. 1999;14(4):1087–9. Available from: https://academic.oup.com/humrep/article/14/4/1087/628799

103. Granot I, Dekel N, Segal I, Fieldust S, Shoham Z, Barash A. Is hydrosalpinx fluid cytotoxic? Human Reproduction. 1998;13(6):1620–4.

104. Bedaiwy MA, Goldberg JM, Falcone T, Singh M, Nelson D, Azab H, et al. Relationship between oxidative stress and embryotoxicity of hydrosalpingeal fluid. Human Reproduction. 2002;17(3):601–4.

105. Strandell A, Waldenstrtim U, Nilsson L, Hamberger L. Hydrosalpinx reduces in-vitro fertilization/embryo transfer pregnancy rates. Human Reproduction. 1994;9(5):861–3.

106. Sung L, Copperman AB, Goldstein M, Lapinski R, Bustillo M, Mukherjee T. Characterization of Cytokines (IL-1a, IL-1b, IL-8, and TNFa) in Human Hydrosalpinx Fluid: A Potential Mechanism for Embryo Toxicity. In: American Society for Reproductive Medicine. 1998. p. S78–S78.

107. Onwuchekwa CR, Oriji V. Hysterosalpingographic (HSG) pattern of infertility in women of reproductive age. Journal of Human Reproductive Sciences. 2017 Jul;10(3):178–84.

108. Groszmann YS, Benacerraf BR. Complete evaluation of anatomy and morphology of the infertile patient in a single visit; the modern infertility pelvic ultrasound examination. Fertility and Sterility. 2016 Jun 1;105(6):1381–93.

109. Abdel-Gadir A. Hysterosalpingo-Contrast-Sonography. In: Illustrated Gynaecology and Infertility Ultrasound. Movement Publishing; 2018.

110. Lőrincz J, Jakab A, Török P. Comparison of current methods of tubal patency assessment. Orvosi Hetilap. 2017 Mar;158(9).

111. Swart P, Mol BWJ, van der Veen F, van Beurden M, Redekop WK, Bossuyt PMM. The accuracy of hysterosalpingography in the diagnosis of tubal pathology: a meta-analysis. Fertility and Sterility. 1995 Sep;64(3).

112. Dijkman AB, Mol BWJ, van der Veen F, Bossuyt PMM, Hogerzeil H v. Can hysterosalpingocontrast-sonography replace hysterosalpingography in the assessment of tubal subfertility? European Journal of Radiology. 2000 Jul;35(1).

113. Papaioannou S, Afnan M, Jafettas J. Tubal assessment tests: still have not found what we are looking for. Reproductive BioMedicine Online. 2007 Jan;15(4).

114. Katz E, Akman MA, Damewood MD, Garcia JE. Deleterious effect of the presence of hydrosalpinx on implantation and pregnancy rates with in vitro fertilization. Fertility and Sterility. 1996;66(1):122–5.

115. Andersen AN, Yue Z, Meng FJ, Petersen K. Low implantation rate after in-vitro fertilization in patients with hydrosalpinges diagnosed by ultrasonography. Human Reproduction. 1994;9(10):1935–8.

116. Blazar AS, Hogan JW, Seller DB, Frishman GN, Wheeler CA, Haning R v. Assisted reproductive fechnology FERTILITY AND STERILITY ~ The impact of hydrosalpinx on successful pregnancy in tubal factor infertility treated by in vitro fertilization. Fertility and Sterility. 1997 Mar;67(3):517–20.

117. Murray CA, Clarke HJ, Lin Tan S. Inhibitory effect of human hydrosalpingeal fluid on mouse preimplantation embryonic development is significantly reduced by the addition of lactate. Human Reproduction vol. 1997;12(11):2504–7.

118. Lass A. What effect does hydrosalpinx have on assisted reproduction? What is the preferred treatment for hydrosalpinges? The ovary's perspective. Human Reproduction. 1999 Apr 8;14(7):1674–7.

119. al Subhi T, Nasser R, Jashnmi A, al Khaduri M, Gowri V, Subhi A, et al. Prevalence of Tubal Obstruction in the Hysterosalpingogram of Women with Primary and Secondary Infertility. Journal of Reproduction & Infertility. 2013;14(4):214–6.

120. Edwards RG, Fishel SB, Cohen J, Fehilly CB, Purdy JM, Slater JM, et al. Factors Influencing the Success of in Vitro Fertilization for Alleviating Human Infertility. Journal of in Vitro Fertilization and Embryo Transfer. 1984;1(I):3–23.

121. Strandell A. The influence of hydrosalpinx on IVF and embryo transfer: a review. Human Reproduction Update. 2000;6(4):387–95.

122. Strandell A, Lindhard A, Waldenstrom U, Thorburn J, Janson PO, Hamberger L. Hydrosalpinx and IVF outcome: a prospective, randomized multicentre trial in Scandinavia on salpingectomy prior to IVF. Human Reproduction [Internet]. 1999;14(11):2762–9. Available from: https://academic.oup.com/humrep/article/14/11/2762/859741

123. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. 2014.

124. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343:d5928.

125. Deeks J, Higgins J, Altman D, on behalf of Cochrane Statistical Methods group. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins J, Thomas J, Chandler J, Cumpston M, Page M, Welch V, editors. Cochrane Handbook for Systematic Reviews of Interventions version 62 (updated February 2021). 6.2. Oxford: Cochrane; 2021.

126. Zolghadri J, Momtahan M, Alborzi S, Mohammadinejad A, Khosravi D. Pregnancy outcome in patients with early recurrent abortion following laparoscopic tubal corneal interruption of a fallopian tube with hydrosalpinx. Fertility and Sterility. 2006 Jul;86(1):149–51.

127. Zhou Y, Jiang H, Zhang WX, Ni F, Wang XM, Song XM. Ultrasound-guided aspiration of hydrosalpinx occurring during controlled ovarian hyperstimulation could improve clinical outcome of in vitro fertilization–embryo transfer. Journal of Obstetrics and Gynaecology Research. 2016 Aug 1;42(8):960–5.

128. Fouda UM, Sayed AM. Effect of ultrasound-guided aspiration of hydrosalpingeal fluid during oocyte retrieval on the outcomes of in vitro fertilisation-embryo transfer: A randomised controlled trial (NCT01040351). Gynecological Endocrinology. 2011 Aug;27(8):562–7.

129. Barmat LI, Rauch E, Spandorfer S, Kowalik A, Sills ES, Schattman G, et al. The Effect of Hydrosalpinges on IVF-ET Outcome. Journal of Assisted Reproduction and Genetics. 1999;16(7):350–4.

130. Kassabji M, Simsb JA, Butlerb L, Muasher SJ. Reduced pregnancy outcome in patients with unilateral or bilateral hydrosalpinx after in vitro fertilization. European Journal of Obstetrics & Gynecology and Reproductive Biology. 1994;56:129–32.

131. Fleming C, Hull MGR. Impaired implantation after in vitro fertilisation treatment associated with hydrosalpinx. British Journal of Obstetrics and Gynaecology. 1996 Mar;103:268–72.

132. Murray DL, Sagoskin AW, Widra EA, Levy MJ. The adverse effect of hydrosalpinges on in vitro fertilization pregnancy rates and the benefit of surgical correction. Fertility and Sterility. 1998;69(1):41–5.

133. Akman MA, Garcia JE, Damewood MD, Watts LD, Katz E. Hydrosalpinx affects the implantation of previously cryopreserved embryos. Human Reproduction [Internet]. 1996;11(5):1013–4. Available from: http://humrep.oxfordjournals.org/

134. Freeman MR, Whitworth CM, Hill GA. Permanent impairment of embryo development by hydrosalpinges*. Human Reproduction. 1998;13(4):983–6.

135. Ng EH-Y, Yeung WS-B, Ho P-C. The Presence of Hydrosalpinx May Not Adversely Affect the Implantation and Pregnancy Rates in In Vitro Fertilization Treatment. Journal of Assisted Reproduction and Genetics. 1997;14(9):508–12.

136. Sharara F, Scott R, Marut E, Queenan JT, Reese M. In-vitro fertilization outcome in women with hydrosalpinx*. Human Reproduction [Internet]. 1996;11(3):526–30. Available from: http://humrep.oxfordjournals.org/

137. Vandromme J, Chasse E, Lejeune B, Rysselberge M van, Delvigne A, Leroy F. Hydrosalpinges in in-vitro fertilization: an unfavourable prognostic feature. Human Reproduction [Internet]. 1995;10(3):576–9. Available from: http://humrep.oxfordjournals.org/

138. Shelton KE, Butler L, Toner JP, Oehninger S, Muasher SJ. Salpingectomy improves the pregnancy rate in in-vitro fertilization patients with hydrosalpinx. Human Reproduction [Internet]. 1996;11(3):523–5. Available from: http://humrep.oxfordjournals.org/

139. Dechaud H, Daures JP, Arnal F, Humeau C, Hedon B. Does previous salpingectomy improve implantation and pregnancy rates in patients with severe tubal factor

infertility who are undergoing in vitro fertilization? A pilot prospective randomized study. Fertility and Sterility. 1998;69(6):1020–5.

140. Goldstein D, Sasaran L, Stadtmauer L, Popa R. Selective salpingostomy-salpingectomy (SSS) and medical treatment prior to IVF in patients with hydrosalpinx. Fertility & Sterility. 1998;70 (3, Suppl 1)(3:S320).

141. Hammadieh N, Coomarasamy A, Ola B, Papaioannou S, Afnan M, Sharif K. Ultrasound-guided hydrosalpinx aspiration during oocyte collection improves pregnancy outcome in IVF: a randomized controlled trial. Human Reproduction. 2008;23(5):1113–7.

142. Kontoravdis A, Makrakis E, Pantos K, Botsis D, Deligeoroglou E, Creatsas G. Proximal tubal occlusion and salpingectomy result in similar improvement in in vitro fertilization outcome in patients with hydrosalpinx. Fertility and Sterility. 2006 Dec;86(6):1642–9.

143. Klock SC, Chang G, Hiley A, Hill J. Psychological distress among women with recurrent spontaneous abortion. Psychosomatics. 1997;38(5):503–7.

144. Rowsell E, Jongman G, Kilby M, Kirchmeier R, Orford J. The psychological impact of recurrent miscarriage, and the role of counselling at a pre-pregnancy counselling clinic. Journal of Reproductive and Infant Psychology. 2001;19(1):33–45.

145. Osmers R. Gynaecological pathology. In: Wladimiroff J, Eik-Nes S, editors. Ultrasound in Obstetrics and Gynaecology. Elsevier; 2009.

146. Griffin N, Grant LA. Gynaecology. In: Griffin N, Grant LA, editors. Grainger & Allison's Diagnostic Radiology Essentials. Elsevier; 2013.

147. Federle MP, Rosado-de-Christenson ML, Raman SP, Carter BW, Woodward PJ, Shaaban AM, editors. Uterus. In: Imaging Anatomy: Chest, Abdomen, Pelvis. 2nd ed. Elsevier; 2017.

148. Levine D, Brown DL, Andreotti RF, Benacerraf B, Benson CB, Brewster WR, et al. Management of asymptomatic ovarian and other adnexal cysts imaged at US: Society of radiologists in ultrasound consensus conference statement. Radiology. 2010 Sep;256(3):943–54.

149. Grimbizis GF, Gordts S, di Spiezio Sardo A, Brucker S, de Angelis C, Gergolet M, et al. The ESHRE/ESGE consensus on the classification of female genital tract congenital anomalies. Human Reproduction. 2013 Aug 1;28(8).

150. Grimbizis GF, di Spiezio Sardo A, Saravelos SH, Gordts S, Exacoustos C, van Schoubroeck D, et al. The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies. Human Reproduction. 2016 Jan;31(1).

151. Kamaya A, Yu PC, Lloyd CR, Chen BH, Desser TS, Maturen KE. Sonographic evaluation for endometrial polyps: The interrupted mucosa sign. Journal of Ultrasound in Medicine. 2016 Nov 1;35(11):2381–7.

152. van den Bosch T, Dueholm M, Leone FPG, Valentin L, Rasmussen CK, Votino A, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: A consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound in Obstetrics and Gynecology. 2015 Sep 1;46(3):284–98.

153. Guerriero S, Condous G, van den Bosch T, Valentin L, Leone FPG, van Schoubroeck D, et al. Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. Ultrasound in Obstetrics and Gynecology. 2016 Sep 1;48(3):318–32.

154. Sayasneh A, Ekechi C, Ferrara L, Kaijser J, Stalder C, Sur S, et al. The characteristic ultrasound features of specific types of ovarian pathology (Review). International Journal of Oncology. 2015 Feb 1;46(2):445–58.

155. The Rotterdam ESHRE/ ASRM-sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Fertility and Sterility. 2004;81(1):19–25.

156. Teede H, Misso M, Costello M, Dokras A, Laven J, Moran L, et al. International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 [Internet]. Melbourne; 2018 Feb [cited 2021 Apr 11]. Available from: monash.edu/medicine/sphpm/mchri/pcos

157. Munro MG, Critchley HOD, Broder MS, Fraser IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. International Journal of Gynecology and Obstetrics. 2011;113(1):3–13.

158. Ng KYB, Cheong Y. Assessment of fallopian tube patency. In: Stewart JA, editor. Subferility, Reproductive Endocrinology and Assisted Reproduction. Cambridge: Cambridge University Press; 2019. p. 55–63.

159. Ranganathan P, Pramesh C, Buyse M. Common pitfalls in statistical analysis: Clinical versus statistical significance. Perspectives in Clinical Research. 2015;6(3):169–70.

160. Fieglar W, Felix R, Langer M, Schultz E. Fat as a factor affecting resolution in diagnostic ultrasound: possibilities for improving picture quality. Eur J Radiol. 1985 Nov;5(4):304–9.

161. Glanc P, O'Hayon BE, Singh DK, Bokhari SAJ, Maxwell C v. Challenges of pelvic imaging in obese women. Radiographics. 2012;32(6):1839–62.

162. Shmulewitz A, Teefey SA, Robinson BS. Factors Affecting Image Quality and Diagnostic Efficacy in Abdominal Sonography: A Prospective Study of 140 Patients. J Clin Ultrasound. 1993;21:623–30.

163. Marci R, Marcucci I, Marcucci AA, Pacini N, Salacone P, Sebastianelli A, et al. Hysterosalpingocontrast sonography (HyCoSy): Evaluation of the pain perception, side effects and complications. BMC Medical Imaging. 2013 Aug 23;13(28).

164. Reis MM, Soares SR, Cancado ML, Camargos AF. Hysterosalpingo contrast sonography (HyCoSy) with SH U 454 (Echovist ®) for the assessment of tubal patency. Human Reproduction. 1998;13(11):3049–52.

165. Wilcox A. Fertility and Pregnancy: An Epidemiologic Perspective. Oxford: Oxford University Press; 2010.

166. Newbatt E, Beckles Z, Ullman R, Lumsden MA. Ectopic pregnancy and miscarriage: summary of NICE guidance. BMJ. 2012 Dec 15;345:40–2.

167. Petrou S, Hippisley-Cox J, Nicodemo C, Daher S, Bolbocean C, Quenby S, et al. Economic costs associated with miscarriage: A secondary analysis of QResearch [Internet]. Oxford; 2020 [cited 2021 Jan 17]. Available from: https://www.qresearch.org/research/approved-research-programs-and-projects/economic-costs-associated-with-miscarriage-a-secondary-analysis-of-qresearch/#h-H2_7

168. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650).

169. GRADE Working Group. GRADE Handbook. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. Cochrane; 2013.

170. Achilli C, Duran-Retamal M, Saab W, Serhal P, Seshadri S. The role of immunotherapy in in vitro fertilization and recurrent pregnancy loss: a systematic review and meta-analysis. Fertility and Sterility. 2018 Nov 1;110(6):1089–100.

171. Wong LF, Porter TF, Scott JR. Immunotherapy for recurrent miscarriage. Cochrane Database of Systematic Reviews. 2014 Oct 21;2014(10).

172. Dan S, Wei W, Yichao S, Hongbo C, Shenmin Y, Jiaxiong W, et al. Effect of Prednisolone Administration on Patients with Unexplained Recurrent Miscarriage and in Routine Intracytoplasmic Sperm Injection: A Meta-Analysis. American Journal of Reproductive Immunology. 2015 Jul 1;74(1):89–97.

173. Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD. A Review of Systemic Corticosteroid Use in Pregnancy and the Risk of Select Pregnancy and Birth Outcomes. Rheumatic Disease Clinics of North America. 2017 Aug;43(3).

174. Areia AL, Fonseca E, Areia M, Moura P. Low-molecular-weight heparin plus aspirin versus aspirin alone in pregnant women with hereditary thrombophilia to improve live birth rate: meta-analysis of randomized controlled trials. Archives of Gynecology and Obstetrics. 2016 Jan 1;293(1):81–6.

175. de Jong PG, Kaandorp S, di Nisio M, Goddijn M, Middeldorp S. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. Cochrane Database of Systematic Reviews. 2014 Jul 4;2014(7).

176. Liu X, Qiu Y, Yu ED, Xiang S, Meng R, Niu K fan, et al. Comparison of therapeutic interventions for recurrent pregnancy loss in association with antiphospholipid syndrome: A systematic review and network meta-analysis. American Journal of Reproductive Immunology. 2020 Apr 1;83(e13219).

177. Zhang T, Ye X, Zhu T, Xiao X, Liu Y, Wei X, et al. Antithrombotic Treatment for Recurrent Miscarriage. Medicine (United States). 2015 Nov 1;94(45):e1732-undefined.

178. Carp H. A systematic review of dydrogesterone for the treatment of recurrent miscarriage. Gynecological Endocrinology. 2015 Jun 1;31(6):422–30.

179. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. Cochrane Database of Systematic Reviews. 2019 Nov 20;2019(11).

180. Lim CED, Ho KKW, Cheng NCL, Wong FWS. Combined oestrogen and progesterone for preventing miscarriage. Cochrane Database of Systematic Reviews. 2013 Sep 25;2013(9).

181. Earl R, Crowther CA, Middleton P. Interventions for hyperthyroidism pre-pregnancy and during pregnancy. Cochrane Database of Systematic Reviews. 2013 Nov 19;2013(11).

182. Rao M, Zeng Z, Zhou F, Wang H, Liu J, Wang R, et al. Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity: A systematic review and meta-analysis. Human Reproduction Update. 2019 May 1;25(3):344–61.

183. Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E. Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. Cochrane Database of Systematic Reviews. 2013 May 31;2013(5).

184. Chen H, Fu J, Huang W. Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history. Cochrane Database of Systematic Reviews. 2016 Jul 25;2016(7).

185. Morley LC, Simpson N, Tang T. Human chorionic gonadotrophin (hCG) for preventing miscarriage. Cochrane Database of Systematic Reviews. 2013 Jan 31;2013(1).

186. Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database of Systematic Reviews. 2017 Nov 29;2017(11).

187. Palomba S, Falbo A, Orio F, Zullo F. Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Fertility and Sterility. 2009 Nov;92(5):1646–58.

188. Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database of Systematic Reviews. 2017 Jun 6;2017(6).

189. Rikken JFW, Kowalik CR, Emanuel MH, Mol BWJ, van der Veen F, van Wely M, et al. Septum resection for women of reproductive age with a septate uterus. Cochrane Database of Systematic Reviews. 2017 Jan 17;2017(1).

190. Lensen SF, Manders M, Nastri CO, Gibreel A, Martins WP, Templer GE, et al. Endometrial injury for pregnancy following sexual intercourse or intrauterine insemination. Cochrane Database of Systematic Reviews. 2016 Jun 14;2016(6).

191. Aleman A, Althabe F, Belizán JM, Bergel E. Bed rest during pregnancy for preventing miscarriage. Cochrane Database of Systematic Reviews. 2005 Apr 20;2005(2).

192. Furber CM, Mcgowan L, Bower P, Kontopantelis E, Quenby S, Lavender T. Antenatal interventions for reducing weight in obese women for improving pregnancy outcome. Cochrane Database of Systematic Reviews. 2013 Jan 31;2013(1).

193. Balogun OO, da Silva Lopes K, Ota E, Takemoto Y, Rumbold A, Takegata M, et al. Vitamin supplementation for preventing miscarriage. Cochrane Database of Systematic Reviews. 2016 May 6;2016(5).

194. De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Cochrane Database of Systematic Reviews. 2015 Dec 14;2015(12).

195. Keats EC, Haider BA, Tam E, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database of Systematic Reviews. 2019 Mar 14;2019(3).

196. Li L, Dou L, Leung PC, Chung TKH, Wang CC. Chinese herbal medicines for unexplained recurrent miscarriage. Cochrane Database of Systematic Reviews. 2016 Jan 14;2016(1).

197. Yang G-Y, Luo H, Liao X, Liu J-P. Chinese herbal medicine for the treatment of recurrent miscarriage: a systematic review of randomized clinical trials. BMC Complementary and Alternative Medicine [Internet]. 2013;13(320):undefined. Available from: http://www.biomedcentral.com/1472-6882/13/320

198. Boelig RC, Barton SJ, Saccone G, Kelly AJ, Edwards SJ, Berghella V. Interventions for treating hyperemesis gravidarum. Cochrane Database of Systematic Reviews. 2016 May 12;2016(5).

199. Brocklehurst P, Gordon A, Heatley E, Milan SJ. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane Database of Systematic Reviews. 2013 Jan 31;2013(1).

200. Brown HC, Smith HJ, Mori R, Noma H. Giving women their own case notes to carry during pregnancy. Cochrane Database of Systematic Reviews. 2015 Oct 14;2015(10).

201. Claire R, Chamberlain C, Davey MA, Cooper SE, Berlin I, Leonardi-Bee J, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews. 2020 Mar 4;2020(3).

202. González R, Pons-Duran C, Piqueras M, Aponte JJ, ter Kuile FO, Menéndez C. Mefloquine for preventing malaria in pregnant women. Cochrane Database of Systematic Reviews. 2018 Nov 14;2018(11).

203. Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, et al. Levothyroxine in Women with Thyroid Peroxidase Antibodies before Conception. New England Journal of Medicine. 2019 Apr 4;380(14).

204. Carp H. A systematic review of dydrogesterone for the treatment of threatened miscarriage. Gynecological Endocrinology. 2012 Dec;28(12):983–90.

205. Devaseelan P, Fogarty PP, Regan L. Human chorionic gonadotrophin for threatened miscarriage. Cochrane Database of Systematic Reviews. 2010 May 12;2010(5).

206. Lee HJ, Park TC, Kim JH, Norwitz E, Lee B. The Influence of Oral Dydrogesterone and Vaginal Progesterone on Threatened Abortion: A Systematic Review and Meta-Analysis. BioMed Research International. 2017;2017.

207. Wahabi HA, Fayed AA, Esmaeil SA, Bahkali KH. Progestogen for treating threatened miscarriage. Cochrane Database of Systematic Reviews. 2018 Aug 7;2018(8).

208. Li L, Dou L, Leung PC, Wang CC. Chinese herbal medicines for threatened miscarriage. Cochrane Database of Systematic Reviews. 2012 May 16;2012(5).

209. al Wattar BH, Murugesu N, Tobias A, Zamora J, Khan KS. Management of first-trimester miscarriage: A systematic review and network meta-analysis. Human Reproduction Update. 2019 May 1;25(3):362–74.

210. Nanda K, Lopez LM, Grimes DA, Peloggia A, Nanda G. Expectant care versus surgical treatment for miscarriage. Cochrane Database of Systematic Reviews. 2012 Mar 14;2012(3).

211. Wen J, Cai QY, Deng F, Li YP. Manual versus electric vacuum aspiration for first-trimester abortion: A systematic review. BJOG: An International Journal of Obstetrics and Gynaecology. 2008 Jan;115(1):5–13.

212. Wu HL, Marwah S, Wang P, Wang QM, Chen XW. Misoprostol for medical treatment of missed abortion: A systematic review and network meta-analysis. Nature Scientific Reports. 2017 Dec 1;7(1664).

213. Webber K, Grivell RM. Cervical ripening before first trimester surgical evacuation for non-viable pregnancy. Cochrane Database of Systematic Reviews. 2015 Nov 10;2015(11).

214. Ghosh J, Papadopoulou A, Devall AJ, Jeffery HC, Beeson LE, Do V, et al. Methods for managing miscarriage: a network meta-analysis. Cochrane Database of Systematic Reviews. 2021 Jun 1;2021(6).

215. Cleeve A, Fønhus MS, Lavelanet A. A systematic review of the effectiveness, safety, and acceptability of medical management of intrauterine fetal death at 14–28 weeks of gestation. International Journal of Gynecology and Obstetrics. 2019 Dec 1;147(3):301–12.

216. Dodd JM, Crowther CA. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. Cochrane Database of Systematic Reviews. 2010 Apr 14;2010(4).

217. Lemmers M, Verschoor MA, Kim BV, Hickey M, Vazquez JC, Mol BWJ, et al. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database of Systematic Reviews. 2019 Jun 17;2019(6).

218. Kim C, Barnard S, Neilson JP, Hickey M, Vazquez JC, Dou L. Medical treatments for incomplete miscarriage. Cochrane Database of Systematic Reviews. 2017 Jan 31;2017(1).

219. Tunçalp Ö, Gülmezoglu AM, Souza JP. Surgical procedures for evacuating incomplete miscarriage. Cochrane Database of Systematic Reviews. 2010 Sep 8;2010(9).

220. May W, Gülmezoglu AM, Ba-Thike K. Antibiotics for incomplete abortion. Cochrane Database of Systematic Reviews. 2007;2007(4).

221. Udoh A, Effa EE, Oduwole O, Okusanya BO, Okafo O. Antibiotics for treating septic abortion. Cochrane Database of Systematic Reviews. 2016 Jul 1;2016(7).

222. Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, et al. The Oxford Levels of Evidence 2 [Internet]. Oxford Centre for evidence-Based Medicine. Oxford; 2011 [cited 2021 Jan 17]. Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence

223. Melo P, Georgiou EX, Johnson N, van Voorst SF, Strandell A, Mol BWJ, et al. Surgical treatment for tubal disease in women due to undergo in vitro fertilisation. The Cochrane database of systematic reviews. 2020 Oct 22;10:CD002125.

224. Chu J, Harb HM, Gallos ID, Dhillon R, Al-Rshoud FM, Robinson L, et al. Salpingostomy in the treatment of hydrosalpinx: A systematic review and meta-analysis. Human Reproduction. 2015 May 22;30(8):1882–95.

225. Mol F, van Mello NM, Strandell A, Strandell K, Jurkovic D, Ross J, et al. Salpingotomy versus salpingectomy in women with tubal pregnancy (ESEP study): An open-label, multicentre, randomised controlled trial. The Lancet. 2014;383(9927):1483–9.

226. Cheng X, Tian X, Yan Z, Jia M, Deng J, Wang Y, et al. Comparison of the fertility outcome of salpingotomy and salpingectomy in women with tubal pregnancy: A systematic review and meta-analysis. PLoS ONE. 2016 Mar 1;11(3).

227. Killick S. Chapter 38 - Ultrasound assessment of fertility. In: Allan P, Baxter G, Weston M, editors. Clinical Ultrasound. 3rd ed. Elsevier; 2011. p. 730–9.

228. Kanters S, Ford N, Druyts E, Thorlund K, Mills EJ, Bansback N. Use of network meta-analysis in clinical guidelines. Bulletin of the World Health Organization. 2016 Oct 1;94(10).

229. Chu JJ, Devall AJ, Beeson LE, Hardy P, Cheed V, Sun Y, et al. Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): a randomised, double-blind, placebo-controlled trial. The Lancet. 2020 Sep;396(10253).

APPENDICES

Appendix 1: Protocol v1.1. for "The role of hydrosalpinx in recurrent miscarriage"

The role of hydrosalpinx in recurrent miscarriage

PROTOCOL

Version 1.1

28th December 2017

Chief Investigator

Professor Arri Coomarasamy

Tel:

Email:

Key contacts:

- The CI is responsible for the medical oversight of the study.
- Professor Arri Coomarasamy is the Director of the Tommy's National Centre for Miscarriage Research
- Dr. Adam Devall is the Trial Manager for Tommy's National Centre for Miscarriage Research:
- Dr. Sean Jennings is the Research Governance and Ethics Manager for the University of Birmingham (Sponsor): researchgovernance@contacts.bham.ac.uk

Table of Contents

The role of hydrosalpinx in recurrent miscarriage study design group 3
Principal Investigator & Chief Investigator 3
Study Design and Management 3
Co-Investigators 3
Background 4
Epidemiology of miscarriage 4
Tubal disease and its effect on reproductive outcomes 4
Detection of tubal disease 5
Rationale for this study 5
Objectives 6
Study Design 6
Population to be studied 6
Inclusion criteria 6
Exclusion criteria 6
Identifying Participants 6
Data to be collected and tests to be performed 6
Outcomes to be measured 7
Method of collection of data and outcomes 7
Consent to participation and feedback of results 8
Dissemination of study results 8
Withdrawal process 8
Patient Journey 8
Accrual and Analysis 9
Sample Size 9
Statistical Analysis 9
Data management and archiving 9
Safety reporting (Adverse Events and Serious Adverse Events) 10
Serious breaches 10
Insurance and indemnity 10
End of study definition 10
Study Oversight and Quality Assurance processes 10
Funding and Sponsorship 10
Study Flow Chart 12
List of References 13

The role of hydrosalpinx in recurrent miscarriage study design group

Principal Investigator & Chief Investigator

Professor Arri Coomarasamy
Professor of Gynaecology, University of Birmingham
Birmingham Women's Hospital

Study Design and Management

Dr Jayasish Ghosh
Clinical Research Fellow and Registrar in Obstetrics and Gynaecology
Birmingham Women's Hospital

Co-Investigators

Dr Ioannis D Gallos
Honorary Clinical Lecturer and Sub-speciality Trainee in Reproductive Medicine and Surgery
Birmingham Women's Hospital

Dr Justin J Chu
Academic Clinical Lecturer and Registrar in Obstetrics and Gynaecology
Birmingham Women's Hospital

Background

Epidemiology of miscarriage

Miscarriage, also known as spontaneous pregnancy loss before the fetus reaches viability, is a common early pregnancy complication. One in five pregnancies miscarries, which equates to over 250,000 miscarriages a year and 38,349 hospital admissions in the UK between April 1st 2015 and March 31st 2016.[1, 7] Miscarriage can be devastating to women and couples trying to conceive. It is a significant source of physical and psychological morbidity for many women and couples, the effects of which can endure for many months.[8] Yet for all the physical and mental sequelae and the economic costs, we have made little progress in treating this distressing condition.

Most miscarriages happen in the first 12 weeks of pregnancy because of sporadic chromosomal abnormalities.[9] However, for women with recurrent miscarriages, there may be genetic factors such as parental chromosomal abnormalities, embryonic chromosomal abnormalities, as well as structural anatomical abnormalities such as congenital uterine malformations causing miscarriage.[10-17] Other risk factors include endocrine disease such as diabetes, systemic and genital infections and thrombophilia such as Anti-Phospholipid Syndrome.[18, 19] The full list is recorded in appendix A for reference. However, despite very thorough investigation (full list of recommended investigations is outlined in Appendix B), a significant proportion of women with recurrent miscarriage will be labelled as unexplained and be left with no definitive answers, treatments or sometimes sadly, hope.[20]

Tubal disease and its effect on reproductive outcomes

C. trachomatis is the most common sexually transmitted infection in the UK.[2] *C. trachomatis* often has no symptoms, but can have serious health consequences, including fallopian tube damage. Untreated *C. trachomatis* infection in pregnancy may increase the risk of miscarriage, preterm birth, low birth weight and stillbirth.[4-6]

A severe form of tubal damage is when the tube is blocked and filled with fluid, a condition called hydrosalpinx. They are classically caused by ascending infections from the lower genital tract such as chlamydia, which cause pelvic inflammatory disease, causing the tubes to appear swollen and enlarged.[21] Hydrosalpinx is associated with a dramatic reduction in the chances of a live birth with assisted reproductive techniques.[22] This is explained by reduced implantation chances and increased pregnancy losses in the presence of a hydrosalpinx.[22] It is therefore strongly recommended that hydrosalpinges are removed or treated by tubal surgery prior to IVF.[23]

It has been suggested that hydrosalpinx may have a causative role in recurrent miscarriage. The biological rationale for this increase in pregnancy losses is not yet well understood. It has been postulated that the hydrosalpinx fluid may be embryotoxic as it can include micro-organisms, endotoxins, cytokines and free radicals causing oxidative stress.[24, 25] This fluid may therefore alter the endometrial receptivity causing a disturbed cytokine cascade, which impedes implantation.[26] Additionally, as the fallopian tube is occluded distally, the hydrosalpinx fluid may drain into the endometrial cavity having a flushing effect on the developing embryo hindering implantation.[27]

Detection of tubal disease

Investigation of suspected tubal disease is currently recommended for women with subfertility by laparoscopy or hysterosalpingography (HSG).[23] Women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered HSG to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion, and it is less invasive and makes more efficient use of resources than laparoscopy.[23] A HSG involves the passage of a radio-opaque contrast media through the female cervix whilst simultaneously taking serial radiographs to examine the patency and free spill of the media into the abdominal cavity. It requires radiographers, specialist radiographic equipment and exposure to radiation. Furthermore, a HSG is performed in a radiology department and requires a radiologist to interpret them.

Where appropriate expertise is available, screening for tubal occlusion using hysterosalpingo-contrast-ultrasonography (HyCoSy) can be considered because it is an effective alternative to HSG for women who are not known to have comorbidities.[23] A HyCoSy is an outpatient procedure which only requires a special contrast media and an USS machine which is usually present in most gynaecological out-patient departments. It is performed at the same time as a pelvic ultrasound, which is recommended for both women with subfertility or recurrent miscarriages.[20, 23] The contrast media is injected through the cervix and its flow into the uterus and out through the fallopian tubes is tracked in real time using the ultrasound machine to detect tubal patency and pathology. A HyCoSy is a standard investigation for fertility problems.

Laparoscopy is an invasive operative investigation where by a fibre optic camera inserted through the umbilicus is used to directly visualise the passage of dye through the fallopian tubes thereby confirming their patency and function. Women who are thought to have comorbidities should be offered laparoscopy and dye so that tubal and other pelvic pathology can be assessed and treated at the same time. Laparoscopy costs the NHS significantly more than HSG or HyCoSy and carries more risk. Costs associated with laparoscopy are in the form of theatre use and staffing, equipment used, recovery facilities and a ward bed.

In addition to the tubal investigations mentioned above, it is also necessary to identify whether women undergoing these investigations have concurrent genital tract infection before undertaking tubal assessment. Tests to diagnose genital *C. trachomatis* infections have evolved rapidly and nucleic acid amplification tests (NAAT), such as polymerase chain reaction (PCR) are now widely available. NAAT has been estimated to have a sensitivity of over 90% and a specificity of 99%, regardless of sampling from a cervical swab or by urine specimen.[28] A screen for *C. trachomatis* infection is recommended before women undergo any form of uterine instrumentation.

Rationale for this study

Miscarriage affects one in five pregnancies and little progress has been made in understanding and treating this distressing condition.[1] *C. trachomatis* is the most common sexually transmitted infection in the UK.[2] *C. trachomatis* infection can have serious health consequences, including fallopian tube damage. Untreated *C. trachomatis* infection and tubal damage have been associated with miscarriage and adverse pregnancy outcomes such as preterm birth, low birth weight and stillbirth.[4-6] A cohort study is needed to establish the prevalence of tubal disease in women with recurrent miscarriages. HyCoSy will be performed to identify tubal disease and establish the magnitude of the problem in the

recurrent miscarriage population. The prognosis of tubal disease on miscarriage and other obstetric outcomes, and the role of medical interventions such as tubal surgery (to treat hydrosalpinx) on reducing miscarriage and adverse obstetric outcomes will also be studied.

Objectives

1. Establish the prevalence of hydrosalpinx in the recurrent miscarriage population.
2. Establish the prognosis of women diagnosed with recurrent miscarriage with concurrent hydrosalpinx.
3. Explore the role of tubal surgery for improving reproductive outcomes in women with recurrent miscarriage population and hydrosalpinx.

Study Design

This is a prospective observational cohort study.

Population to be studied

Potential participants will be approached at the Tommy's recurrent miscarriage clinic held at the Birmingham Women's Hospital.

Inclusion criteria

- Age 18-45
- Women diagnosed with recurrent miscarriage i.e. 2 or more miscarriages
- Ability to give informed consent

Such a wide inclusion criteria will enable a true assessment of the prevalence of hydrosalpinges in the recurrent miscarriage population.

Exclusion criteria

- Allergy to contrast media used for Hysterosalpingo-contrast-sonogram
- Allergy to sonographic gel used for ultrasound scanning
- Anatomical anomaly meaning transvaginal ultrasound scan not possible
- Stenosed/occluded cervix meaning contrast media unable to be introduced via cervix
- Inability to give informed consent
- Pregnant at the time of recruitment
- Declined recruitment

Identifying Participants

Patients will have been given the patient information leaflet prior to their appointment, when they are sent their appointment details letter.

All women presenting to the clinic will be screened for the eligibility criteria by the routine healthcare provider. They will then be approached by Dr Jayasish Ghosh or one of the members of the research team and offered recruitment into the study.

Data to be collected and tests to be performed

- Genital infection screen – This is required as per national guidance prior to any uterine instrumentation to reduce the risk of subsequent pelvic inflammatory disease during

Hysterosalpingo-contrast-sonography. The self-taken vulvovaginal swab and one high vaginal swab will then be sent to the microbiology laboratory of the Birmingham Women's Pathology department and will undergo testing for active infection causing bacteria for example *C. Trachomatis, N. Gonorrhoea, C. Albicans* or bacterial vaginosis. These tests will be in the form of microscopy, culture and sensitivities, polymerase chain reaction and Nugent's scoring. The storage and testing these swabs will be managed in line the Human Tissue Act, 2004.

- To establish the first objective of prevalence, recruited patients will be screened with a Hysterosalpingo-contrast-sonogram (HyCoSy) for the presence or absence of hydrosalpinges.

Outcomes to be measured

- To establish the second objective of prognosis of women with recurrent miscarriage and concurrent hydrosalpinges, pregnancy outcome data will be collected from both groups of patients (patients who screen positive and those who screen negative for hydrosalpinges). Specifically this will include:
    1. Biochemical pregnancy – a positive pregnancy test either on urine or serum pregnancy testing before ultrasound evidence of a gestational sac
    2. Clinical pregnancy – a pregnancy confirmed by evidence of a fetal heartbeat on ultrasound scan or using ultrasound parameters (ultrasound visualization of a gestational sac, embryonic pole with heartbeat).
    3. Pregnancy loss and at what gestation the pregnancy was lost – if unfortunately the patient suffered from a further miscarriage or still birth, the gestation in weeks of the loss will be noted
    4. Ectopic pregnancy – if a clinical pregnancy is seen on ultrasound scan but its location of implantation has taken place outside the uterine cavity, this is known as an ectopic pregnancy. Ectopic pregnancies are usually inside the fallopian tube although rarely they can be abdominal, ovarian or cervical.
    5. Live births – if fortunately a patient has a live birth this will be noted.
- To explore the role of tubal surgery, the same pregnancy outcomes listed above will be collected for the group of patients that were treated by their usual healthcare provider with surgery for their hydrosalpinges.

Method of collection of data and outcomes

- The genital infection screen will be performed by taking a self-taken vulvovaginal swab and a high vaginal swab after written informed consent has been gained. The high vaginal swab will be taken by Dr Jayasish Ghosh, a General Medical Council and Royal College of Obstetricians and Gynaecologists registered registrar who is fully competent in such a procedure.
- The presence or absence of hydrosalpinges will be noted at HyCoSy which will be performed after recruitment and written informed consent has been gained. A urine pregnancy test will also be performed prior to the HyCoSy to ensure the patient is not unknowingly already pregnant which would exclude them from the study. The HyCoSy and pregnancy test will be performed by Dr Jayasish Ghosh, a General Medical Council and Royal College of Obstetricians and Gynaecologists registered registrar who is fully competent in such a procedure.
- The pregnancy outcome data listed above will be collected via a telephone consultation or email correspondence, conducted at 6 months and 12 months either post HyCoSy or post

treatment. Should the patient not recall all of the information needed, she will be consented to examine her hospital patient records. Should the patient have had treatment at a different hospital trust, she would also have been consented to collect the specific information needed directly from that particular hospital's patient records.

Consent to participation and feedback of results

- The conduct of this study will be in accordance with the principles of Good Clinical Practice. All potential participants will be offered a patient information leaflet as well as a copy of the consent form. Participants will be made aware that they can withdraw from the trial at any stage and have their information destroyed.
- Patients will be informed of the results of their genital infection screen and appropriate treatment will be provided as necessary as per Birmingham Women's Hospital antimicrobial prescribing guidelines.
- Patients will also be informed if their pregnancy test performed prior to HyCoSy is positive as they will no longer be able to take part in the study.
- HyCoSy findings will also be shared with the participants at the time of the scan. Any HyCoSy findings that may require urgent gynaecological attention will be referred to the on call gynaecology team at the Birmingham Women's Hospital with the patient's consent. Any other ultrasound findings that require non urgent follow up, will be shared with the GP or routine healthcare provider, with the patient's consent.

Dissemination of study results

The results of the study in terms of the prevalence of hydrosalpinges in the recurrent miscarriage population and the prognosis of women with recurrent miscarriage and concurrent hydrosalpinx will be disseminated to all participants via an email newsletter at the conclusion of the study. The results of comparing outcomes between patients who were treated for their hydrosalpinges versus those who were not, will be also be disseminated to all study participants and those who were not treated will be offered discussion about treatment after the conclusion of the study if treatment shows significant benefit.

Withdrawal process

Participants will be informed that they are able to withdraw from the study at any point without giving a reason and without any impact on their care, however, information gathered up until that point may be still used in the study.

Patient Journey

The patient will be sent the patient information leaflet at the same time as they receive the appointment letter thus ensuring sufficient time to read the written information related to the study before consent is taken. Written informed consent will be taken by good clinical practice trained research midwives or Dr Jayasish Ghosh, a General Medical Council and Royal College of Obstetricians and Gynaecologists registered registrar who is fully competent at taking consent and is also good clinical practice trained.

If a patient consents to participation, they will have the swabs performed as detailed in the method of collection of data and outcomes section above. If the swabs show an infection this will be treated

as per the Birmingham Women's Hospital microbiology prescribing guidelines. At a subsequent appointment they will have a HyCoSy to detect the hydrosalpinges instead of their usual transvaginal pelvic ultrasound scan. A HyCoSy, as detailed in the background section above, incorporates a transvaginal ultrasound scan but is more detailed due to the use of contrast media to detect tubal and uterine pathology which may not be visible on normal transvaginal ultrasound. The result of which will be fed back to the patient and their usual clinician. They will then discuss with this clinician any treatment that maybe required.

If a hydrosalpinx is detected they will discuss with their usual clinician whether tubal surgery and what type would be appropriate. Surgery would then be carried out in the usual manner by the usual clinician. All patients would now be in one of three groups, those with no hydrosalpinx, those with a hydrosalpinx who did not have surgical treatment and those with a hydrosalpinx who did have surgical treatment of their hydrosalpinx. All three cohorts will then be followed up for 12 months as detailed in the method of collection of data and outcome section above. A pictorial representation of the patient journey is shown below in the study flow chart section.

Accrual and Analysis

Sample Size

We will attempt to recruit approximately 203 patients. For a prevalence survey in a condition where the prevalence is unknown, but it is not expected to be higher than 25% for obtaining a 95% level of confidence and precision at 0.05 we have estimated that 184 patients are required. To account for up to a 10% level of attrition, 203 patients should be recruited.

Statistical Analysis

For the prevalence survey of hydrosalpinx in the recurrent miscarriage population data will be presented using descriptive statistics. We will examine the prevalence data within subgroups created from clinical characteristics for example age, body mass index, previous sexually transmitted infections to identify high risk groups for hydrosalpinx.

For the comparison of the cohorts we will report numbers of individuals at each stage of study e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. The reasons for non-participation at each stage will be described. We will also describe the characteristics of study participants (e.g. demographic, clinical) and potential confounders (e.g. age, body mass index.) We will indicate the number of participants with missing data for each variable of interest and compute data for missing covariates using maximum likelihood estimation. We will summarise follow-up time (e.g. average and total amount) and report numbers of outcome events over time for each cohort. We will report unadjusted relative risk estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. at the 95% confidence interval). We will endeavour to translate estimates of relative risk into absolute risk for a meaningful time period. Subgroup analyses will be also performed according to the risk stratification described above.

Data management and archiving

The swab results and ultrasound records will be kept in locked surroundings at all times at the Birmingham Women's Hospital NHS Foundation Trust. A separate log will be kept which connects the patient identifiable data with the study allocation number and this will be destroyed at the end of the study period. Information will be collected on secured computers and all research team members will have had prior training in Good Clinical Practice.

All data originating from this research will be kept in secured, locked surroundings in the Academic Department of Birmingham Women's Hospital. Electronic data will be held on the University of Birmingham Network and it will be accessed through University of Birmingham computers. All results, records and data will be managed in line with the Data Protection Act, 1998 and the Human Tissue Act, 2004.

Safety reporting (Adverse Events and Serious Adverse Events)

Adverse events (AE) are defined as any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease. Occurrence of AEs will be recorded and reported to chief investigator. Any SAE will also be recorded in the study notes.

When an AE has occurred which is suspected to be a potential SAE, the Chief Investigator will assess the causality and severity of the AE. If the AE is confirmed as being a SAE, the CI will follow the University of Birmingham Standard Operating Procedures for SAE reporting, including reporting to the Sponsor. Follow-up of the event will continue until the event is considered resolved by all parties involved or a final outcome has been reached.

Serious breaches

In the unlikely event that a Serious Breach occurs, standard University of Birmingham procedures and SOPs for Serious Breach reporting will be followed.

Insurance and indemnity

The University of Birmingham purchases Clinical Trials Cover, which provides automatic cover for all Clinical Trials including those where the University accepts responsibility as sponsor, for any harm that comes about due to the University's, or its staff's negligence in relation to the design or management of the trial. In some cases, cover can also be provided in the case of non-negligent harm to participants.

End of study definition

Within 90 days of the final endpoint assessment of the final participant the main REC will be notified of the study's end and a summary of the clinical study report will be provided within 12 months of the end of the study. The study is expected to last three years.

Study Oversight and Quality Assurance processes

The Chief Investigator will oversee the quality of the study, and the study team will allow representatives of the Sponsor to monitor the study, including access to source documents as requested.

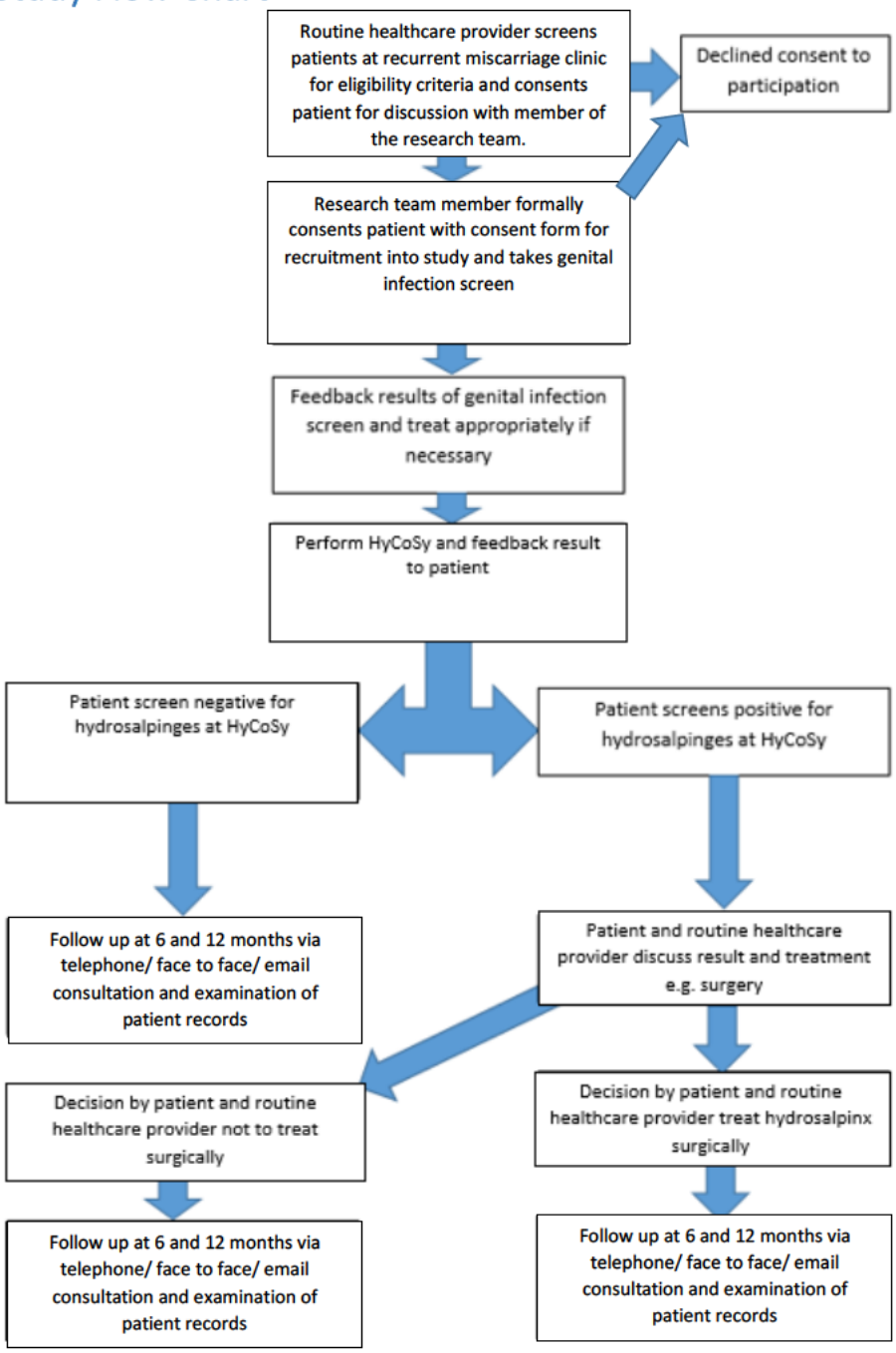
Funding and Sponsorship

Study funding is provided by Tommy's a UK charity that funds research into miscarriage, stillbirth and premature birth. *Tommy's National Centre for Miscarriage Research* is directed from The University

of Birmingham by Professor Arri Coomarasamy but jointly hosted by three other UK universities, namely Imperial College London and The University of Warwick and is based at four NHS hospitals in Birmingham, Coventry and London. The partner institutions work closely with the University of Birmingham to ensure synergy and added value, whilst a vibrant programme of joint research meetings enables junior and senior colleagues to share disciplinary expertise and research news. The centre is seeking to understand why miscarriage happens, if it is likely to happen again, how to prevent it, and how to provide appropriate aftercare.

The University of Birmingham will be sponsoring this study (sponsorship reference number RG_ 17-150). *The University of Birmingham* is characterised by a tradition of innovation. Research at the University has broken new ground, pushed forward the boundaries of knowledge and made an impact on people's lives. The University was ranked 15th in the UK and 82nd in the world in the QS World University Rankings for 2016-17.

Study Flow Chart



List of References

1. Miscarriage Association. *Background information, Miscarriage.* Available from: https://www.miscarriageassociation.org.uk/media-queries/background-information/ [Accessed July 13th 2017]
2. Public Health England. *Sexually Transmitted Infections and Chlamydia Screening in England, 2016*. 2017. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/617020/Health_Protection_Report_STIs_NCSP_2017.pdf [Accessed: July 13th 2017]
3. Mamoun Kassabji, Jerry A. Sims, Lisa Butler, Suheil J. Muasher Reduced pregnancy outcome in patients with unilateral or bilateral hydrosalpinx after in vitro fertilization. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 1994; 56(2): 129-132. Available from: http://www.sciencedirect.com/science/article/pii/0028224394902690 [Accessed July 13th 2017]
4. Giakoumelou S, Wheelhouse N, Cuschieri K, Entrican G, Howie SE, Horne AW. The role of infection in miscarriage. *Hum Reprod Update*. 2016; 22(1): 116-33. doi:10.1093/humupd/dmv041.
5. Gravett MG, Nelson HP, DeRouen T, Critchlow C, Eschenbach DA, Holmes KK. Independent Associations of Bacterial Vaginosis and Chlamydia trachomatis Infection With Adverse Pregnancy Outcome. *JAMA.*1986; 256(14):1899-1903. doi:10.1001/jama.1986.03380140069024
6. Martin DH, Koutsky L, Eschenbach DA, Daling JR, Alexander ER, Benedetti JK, Holmes KK. Prematurity and Perinatal Mortality in Pregnancies Complicated by Maternal Chlamydia trachomatis Infections. *JAMA.*1982; 247(11):1585-1588. doi:10.1001/jama.1982.03320360035027
7. NHS Digital. *Hospital Maternity Activity 2015-2016.* 2016. Available from: http://content.digital.nhs.uk/searchcatalogue?productid=23494&q=%22nhs+maternity+statistics%22&topics=0%2fHospital+care&sort=Relevance&size=10&page=1#top [Accessed July 13th 2017]
8. Ingrid H. Lok, Richard Neugebauer, Psychological morbidity following miscarriage. *Best Practice & Research Clinical Obstetrics & Gynaecology.* 2007; 21(2): 229-247. doi:10.1016/j.bpobgyn.2006.11.007
9. M. Goddijn, N.J. Leschot. Genetic aspects of miscarriage. *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2000; 14(5): 855-865. Available from: http://dx.doi.org/10.1053/beog.2000.0124. [Accessed July 13th 2017]
10. de Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. *Hum Reprod.* 1990; 5(5): 519–28.
11. Clifford K, Rai R, Watson H, Regan L. An informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases. *Hum Reprod*. 1994; 9(7) :1328–32.
12. Mary D. Stephenson, Sony Sierra. Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. *Hum Reprod.* 2006; 21(4): 1076-1082. doi: 10.1093/humrep/dei417

13. Franssen MTM, Korevaar JC, van der Veen F, Leschot NJ, Bossuyt PMM, Goddijn M. Reproductive outcome after chromosome analysis in couples with two or more miscarriages: case-control study. *British Medical Journal*. 2006; 332(7544): 759-763. doi:10.1136/bmj.38735.459144.2F.

14. Carp, Howard et al. Karyotype of the abortus in recurrent miscarriage. *Fertility and Sterility*. 2001; 75(4): 678 – 682. Available from: http://dx.doi.org/10.1016/S0015-0282(00)01801-X [Accessed July 13th 2017]

15. M.D. Stephenson, K.A. Awartani, W.P. Robinson. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case–control study. *Hum Reprod*. 2002; 17(2): 446-451. doi: 10.1093/humrep/17.2.446

16. Grigoris F. Grimbizis, Michel Camus, Basil C. Tarlatzis, John N. Bontis, Paul Devroey. Clinical implications of uterine malformations and hysteroscopic treatment results. *Hum Reprod Update.* 2001; 7(2): 161-174. doi: 10.1093/humupd/7.2.161

17. R. Salim, L. Regan, B. Woelfer, M. Backos, D. Jurkovic. A comparative study of the morphology of congenital uterine anomalies in women with and without a history of recurrent first trimester miscarriage. *Hum Reprod.* 2003; 18(1): 162-166. doi: 10.1093/humrep/deg030

18. U Hanson et al. Relationship between Haemoglobin A1C in early type 1 (insulin-dependent) diabetic pregnancy and the occurrence of spontaneous abortion and fetal malformation in Sweden. *Diabetologia.* 1990; 33(2): 100-104.

19. R.S Rai, K. Clifford, H. Cohen, L. Regan; High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. *Hum Reprod.* 1995; 10(12): 3301-3304. doi: 10.1093/oxfordjournals.humrep.a135907

20. Regan L, Backos M, Rai R. *The Investigation and Treatment of Couples with Recurrent First trimester and Second-trimester Miscarriage*. Royal College of Obstetricians and Gynaecologists. Green-top Guideline No. 17. April 2011. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_17.pdf [Accessed July 13th 2017]

21. Willard Cates, Judith N. Wasserheit. Genital chlamydial infections: Epidemiology and reproductive sequelae. *American Journal of Obstetrics and Gynecology*. 1991; 164(6): 1771-1781. Available from: http://www.sciencedirect.com/science/article/pii/000293789190559A?showall%3Dtrue%26via%3Dihub [Accessed July 13th 2017]

22. Hulusi B Zeyneloglu, Aydin Arici, David L Olive. Adverse effects of hydrosalpinx on pregnancy rates after in vitro fertilization–embryo transfer. *Fertility and Sterility.* 1998; 70(3): 492-499.

23. National Institute for Health and Care Excellence. *Fertility problems: assessment and treatment for people with fertility problems.* NICE Clinical guideline No. 156. February 2013. Available from: https://www.nice.org.uk/guidance/cg156/evidence/full-guideline-pdf-188539453 [Accessed July 13th 2017]

24. A Strandell, A Sjögren, U Bentin-Ley, J Thorburn, L Hamberger, M Brännström. Hydrosalpinx fluid does not adversely affect the normal development of human embryos and implantation in vitro. *Hum Reprod.* 1998; 13(10): 2921-2925. doi: 10.1093/humrep/13.10.2921

25. Mohamed A. Bedaiwy, Jeffrey M. Goldberg, Tommaso Falcone, Mamta Singh, David Nelson, Hamdy Azab, Xia Wang, Rakesh Sharma. Relationship between oxidative stress and

embryotoxicity of hydrosalpingeal fluid. *Hum Reprod* 2002; 17(3): 601-604. doi: 10.1093/humrep/17.3.60

26. Sung, L., Copperman, A.B., Goldstein, M., Lapinski, R., Bustillo, M. and Mukherjee, T. Characterization of cytokines (IL-1α, IL-1β, IL-8, and TNF-α) in human hydrosalpinx fluid: a potential mechanism for embryo toxicity (abstract). *Fertil. Steril.* 1997; 1001(1997): S78
27. Mansour RT, Aboulghar MA, Serour GI, Riad R. Fluid accumulation of the uterine cavity before embryo transfer: a possible hindrance for implantation. *Journal of Assisted Reproduction and Genetics*. 1991; 8(3): 157-159.
28. J. R. Papp, J. Schachter, C. A. Gaydos, B. Van Der Pol. *Recommendations for the Laboratory-Based Detection of Chlamydia trachomatis and Neisseria gonorrhoeae*. Centres for Disease Control and Prevention. 63(RR02). March 2014. Available from https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6302a1.htm [Accessed July 13th 2017]

Appendix 2: Patient information sheet v1.1 for "The role of hydrosalpinx in recurrent miscarriage"

PATIENT INFORMATION SHEET

The role of hydrosalpinx in recurrent miscarriage

Thank you for reading this leaflet.

We would like to invite you to take part in a study to investigate whether hydrosalpinx is associated with recurrent miscarriage. A hydrosalpinx is an abnormal swelling of a damaged fallopian tube. The fallopian tube carries the egg from the ovary (where it is stored and released), towards the uterus where it will meet the sperm. Hydrosalpinges can be caused by infections such as Chlamydia, infection of the pelvis, previous abdominal surgery and endometriosis.

Before you decide whether to take part we would like you to understand why the research is being done and what it will involve. Please take time to read this information leaflet. One of our team will go through the information sheet with you and answer any questions you may have.

What is the purpose of the study?

The aim of the study is to improve our understanding of why women maybe suffering from recurrent miscarriage and what we can do to help them.

We aim to find out;

1. How common hydrosalpinx is amongst women with recurrent miscarriage.

2. If women with hydrosalpinx are more likely to miscarry

3. If women with hydrosalpinx and recurrent miscarriage benefit from surgical treatment.

The information from this study may benefit all women who have suffered from miscarriage.

Why have I been invited?

Understanding why some women suffer from more than 1 miscarriage will help us to better treat this distressing condition. You have been invited to take part as you have been referred to our clinic because you have unfortunately suffered from recurrent miscarriage.

Do I have to take part and can I change my mind?

It is completely up to you to decide if you want to take part in the study or not. If you agree to take part we will request that you sign a written consent form. However, if you change your mind you can withdraw from the study at any time, without having to give a reason. Your decision will be documented and signed by a member of staff. Your choice will not affect the standard of your medical care in any way.

What will happen if I choose to take part?

After signing the consent form and with your agreement we will inform your GP that you have chosen to participate in this study. You will be given a dedicated telephone number to contact the research team on. We will take some routine genital swabs to check for infections and treat the infection if any is found.

At the next appointment we will perform a specialised internal ultrasound scan to look at your pelvic anatomy called a Hysterosalpingo-contrast Sonogram or HyCoSy for short. If we find any abnormalities that are outside of the scope of this study, with your consent, we will pass the information onto the relevant healthcare team.

If a hydrosalpinx (a swollen damaged fallopian tube) is not found, with your consent, we will arrange a telephone/ face to face/ email consultation in 6 months and 12 months to see if you have managed to fall pregnant and what the outcome of the pregnancy was.

If a hydrosalpinx was found, we will inform you and your normal doctor who is looking after you in the recurrent miscarriage clinic. They will discuss and decide in conjunction with yourself, whether to treat the hydrosalpinx which may include surgery. We will then arrange, with your consent, a telephone/ face to face/ email consultation in 6 and 12 months to see if you have managed to fall pregnant and what the outcome of the pregnancy was, whether you have had treatment or not.

If you have a hydrosalpinx but opted not to have treatment, at the end of the study if we find out that treatment of hydrosalpinges does have benefits in terms of reducing the risk of further miscarriage, you will be given the option of re-discussing treatment with the doctor looking after you in the recurrent miscarriage clinic. Please be assured that information collected in the study will remain strictly confidential, adhering to all applicable University of Birmingham and Birmingham Women's Hospital policies and procedures.

What samples am I being asked to donate?

This study will require you to donate 2 swabs.

How will the samples be collected?

The samples will be collected by using standard healthcare procedures at our hospital.

What will happen to the samples I donate?

Each donated sample will be labelled with your individual details and transported in an appropriate container to a laboratory for immediate use and analysis or storage as per the Birmingham Women's Hospital Pathology Laboratory standard operating procedure and in compliance with the Human Tissue Act 2004. The two swabs will be analysed for active infection at the Birmingham Women's Hospital.

What tests will be done to the donated samples?

All donated samples will never be used for anything except ethically approved research to better understand miscarriage. The swabs will include a self-taken vulvovaginal swab and a high-vaginal swab. The two swabs will undergo testing for current infection. The results of the swabs and scans will be stored indefinitely on secure information systems at The Birmingham Women's Hospital, as would any normal swabs or scans that occur during your treatment.

Who can look at my information?

Your consent form will be filed in the study site file. The results of the tests will be viewed by the Tommy's research team, who are outside of the direct care team, as well as the direct care team and all clinical information will be kept strictly confidential. Your email address will be destroyed after the study has been completed. Relevant data collected during the study, may be looked at by individuals from the Birmingham Women's and Children's NHS Foundation Trust, the University of Birmingham, or from regulatory authorities, where it is relevant to your taking part in this research.

Do I have any rights to the research?

If you participate in our research, you will donate any samples as an altruistic gift to help us to find out why miscarriage happens and potentially to find ways to help avoid or treat it in the future. You will not be entitled to restrict the particular questions that the research seeks to answer, and in the unlikely event that any findings are patented for commercial application then you will not be paid.

What are the benefits from participating in the study?

If you choose to participate in this study you will receive a more detailed scan called a Hysterosalpingo-contrast-sonogram or HyCoSy and extra screening for infection. If a hydrosalpinx is found on scan you may be offered surgery to treat this which may reduce the risk of suffering a further miscarriage in the future. You will be contributing towards the knowledge of the causes of recurrent miscarriage which may help develop future treatments for this condition.

What are the disadvantages of participating in the study?

Apart from the inconvenience of having additional tests for infection, a more detailed internal ultrasound scan called a HyCoSy, the time for 2 telephone/ face to face/ email consultations and any emotional distress caused by recalling any traumatic events there are no disadvantages of participating in this study. It is current normal practice during investigations for recurrent miscarriage to have an internal ultrasound scan. There is no additional risk from this scan to yourself when compared to current practices during fertility investigations.

What will happen at the end of the study?

We anticipate that this research study will run for 3 years. As and when our research findings are published, we will make them available on the Tommy's website and you may be emailed a summary of the findings if you provide an email address. If any research material is left in storage at the end of the study, it will be transferred to an ethically regulated research bank.

Who is organising and funding the research?

Within Birmingham Women's Hospital this research is coordinated by Tommy's National Centre for Miscarriage Research. The research is funded by Tommy's charity, who wish to advance work in this area. Tommy's charity makes independent choices about which research projects to support, and has chosen to support our early pregnancy research. The Tommy's National Centre for Miscarriage Research is a collaboration between the University of Birmingham, University of Warwick and Imperial College London and their associated NHS hospitals. The charity insists that any funded project has received appropriate ethical consideration.

Who is providing the insurance for the research?

The study is sponsored by The University of Birmingham (RG_17-150). The University purchases Clinical Trials Cover, which provides automatic insurance cover for all Clinical Trials including those where the University accepts responsibility as sponsor, for any harm that comes about due to the University's, or its staff's negligence in relation to the design or management of the trial. In some cases, cover can also be provided in the case of non-negligent harm to participants.

Who has reviewed the study?

All research projects must be approved by a Research Ethics Committee. This project has also been peer reviewed by Prof T J Clark – Honorary Professor of Gynaecology at Birmingham Women's Hospital.

For further information

You can discuss the details of this study with:

Professor Arri Coomarasamy (Professor of Gynaecology at University of Birmingham),

Dr Jay Ghosh (Clinical Research Fellow and Registrar in Obstetrics and Gynaecology)

Contac

Email:

For emotional/ bereavement support

Our specialist bereavement support team are here to support you and your family through difficult times. They offer a variety of facilities to help you to cope with loss. You can telephone the bereavement team on 0121 623 6882 or 07814 20 84 35. Their office hours are 8.30am to 4.30pm Monday to Friday. Outside of these hours you can leave a message and they will get back to you as soon as possible. Other organisations that you may find helpful include:

- **Tommy's**
  ww.tommys.org
- **Miscarriage Association**
  www.miscarriageassociation.org.uk

Concerns & Complaints

If you have any concerns or complaints about this study which cannot be answered by contacting either the mobile or email address above, you can contact the sponsor's representative or the Patient Advice and Liaison Service whose contact details are listed below.

Sponsor's Representative

Dr Sean Jennings - Research Governance and Ethics Manager for the University of Birmingham

Tel -

Email - researchgovernance@contacts.bham.ac.uk

Patient Advice and Liaison Service (PALS) for Birmingham Women's Hospital

The PALS office can be found in the front of the house area of the hospital.

Tel - 0121 627 2747

Website - http://www.bwnft.nhs.uk/patients-visitors/patient-advice-and-information-centre

Appendix 3: Patient consent form v1.1 for "The role of hydrosalpinx in recurrent miscarriage"

UNIVERSITY OF BIRMINGHAM

Tommy's National Centre for Miscarriage Research

NHS Birmingham Women's and Children's NHS Foundation Trust

The Role of Hydrosalpinx in Recurrent Miscarriage Study

Participant Consent Form

Please initial each box to confirm consent

confirm that have read and understand the information sheet (v1 1 28-Dec-2017) for the above study have had the opportunity to consider the information ask questions and these have been answered satisfactorily	☐
understand that my participation is voluntary and that if take part am free to withdraw at any time without giving a reason and without my treatment or legal rights being affected	☐
understand that if withdraw from the study anonymised information already collected about me to the stage of withdrawal may be used in the final analysis	☐
understand what is involved in the study and will be happy to undergo genital swabs and a hysterosalpingo-contrast-sonogram which will involve a transvaginal ultrasound scan	☐
understand that will be contacted via telephone or email in approximately 6 and 12 months' time to ask me about any future pregnancies, miscarriages, ectopic pregnancies live births and stillbirths	☐
understand that my results as well as my patient records will be viewed by the research team who are outside of my direct care team as well as my direct care team and that all clinical information will be kept confidential	☐
understand that if subsequently seek treatment related to early pregnancy or obstetric problems in another local hospital that the research team may obtain information relevant to the study from my patient records at that hospital	☐
give permission for my GP to be contacted and informed of my participation in this study	☐
understand and agree that the research team may wish to contact me via telephone email or letter in order to gather or distribute further information if required	☐
consent for any of my remaining samples to be used in other ethically approved studies along with my anonymised medical data	☐
consent for any of my anonymised samples and clinical data to be sent to external laboratories in the UK and outside the UK for additional analysis	☐
consent for any of my samples which are left in storage at the end of the study to be transferred to an ethically regulated research bank YES ☐ NO ☐	☐

IRAS ID: 232650, UoB Research Governance Reference Number: RG_17-150
Participant consent form v1.1, 28-Dec-2017

I understand that re evant data co ected dur ng the study, may be ooked at by nd v dua s from the B rm ngham Women's and Children's NHS Foundat on Trust, the Un vers ty of B rm ngham, from regu atory author t es or from the NHS Trust, where t s re evant to my tak ng part n th s research. I g ve perm ss on for these nd v dua s to have access to th s data. ☐

I agree to part c pate n the ro e of hydrosa p nx n recurrent m scarr age study. ☐

……	……	……..
Name of Pat ent n B ock Cap ta s	Date	S gnature
……	……	……..
Name of Person tak ng consent	Date	S gnature

Study Number ……..

Email Address…….....

Contact Telephone Number……..

Appendix 4: GP information sheet v1.1 for "The role of hydrosalpinx in recurrent miscarriage"

GP NAME

PRACTICE NAME

PRACTICE ADDRESS

DATE

Dear Dr GP NAME,

Re: The role of hydrosalpinx in recurrent miscarriage

Name	
DOB	
Address	

Your patient has kindly agreed to take part in a study looking at the role of hydrosalpinx in recurrent miscarriage at the Tommy's National Centre for Miscarriage Research. This research is a prospective cohort study; your patient has agreed to donate samples and undergo a Hystero-salpingo-sonogram for research purposes and for the research team to follow-up their progress via their medical notes and telephone and email correspondence. This study is funded by the Tommy's charity and is ethically and regulator approved.

We do not anticipate that the participation of your patient in our study will affect your care for her, and we will not ask you to carry out any study-related investigations.

This letter is for information only.

If you would like any further details, please feel free to contact Dr Jayasish Ghosh – Clinical Research Fellow on

Thank you for your support.

Yours sincerely,

Dr Jayasish Ghosh

IRAS ID: 232650, UoB Research Governance Reference Number: RG_17-150
GP Information Letter v1.1, 28-Dec-2017

Appendix 5: Confirmation of sponsorship from The University of Birmingham for "The role of hydrosalpinx in recurrent miscarriage"

UNIVERSITY OF BIRMINGHAM

FINANCE OFFICE

Prof A Coomarasamy
Institute of Metabolism and Systems Research
University of Birmingham

Tuesday, 14 November 2017

Dear Prof Coomarasamy

Project Title:	The role of hydrosalpinx in recurrent miscarriage
Sponsor Reference:	RG_17-150
ERN reference:	ERN_17-1086

Under the requirements of Department of Health Research Governance Framework for Health and Community Care, the University of Birmingham agrees to act as Sponsor for this project. Sponsorship is subject to you obtaining a favourable ethical opinion and NHS R&D management approval where appropriate.

As Chief Investigator, you must ensure that local study recruitment does not commence until all applicable approvals have been obtained. Where a study is or becomes multi-site you are responsible for ensuring that recruitment at external sites does not commence until local approvals have been obtained.

Following receipt of all relevant approvals, you should ensure that any subsequent amendments are notified to the Sponsor, REC and relevant NHS R&D Office(s), and that an annual progress report is submitted to the Sponsor, REC and NHS R&D departments where requested.

Please ensure you are familiar with the University of Birmingham Code of Practice for Research (http://www.birmingham.ac.uk/Documents/university/legal/research.pdf) and any appropriate College or School guidelines.

Finally please contact researchgovernance@contacts.bham.ac.uk should you have any queries.

You may show this letter to external organisations.

Yours sincerely

pp Dr Sean Jennings
Head of Research Governance and Ethics
Research Support Group

Cc Dr Jayasish Ghosh

University of Birmingham Edgbaston Birmingham B15 2TT United Kingdom
w: www.finance.bham.ac.uk

Appendix 6: IRAS form for "The role of hydrosalpinx in recurrent miscarriage"

Full Set of Project Data IRAS Version 5.5.2

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
The role of hydrosalpinx in recurrent miscarriage

1. Is your project research?

(•) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal pro t and an investigatio medical device

( ) Other clinical trial to study a novel intervention or randomise ical trial to compare interventions in clinical practice

(•) Basic science study involving procedures with human pa ticipants

( ) Study administering questionnaires/inte ws for quan tative analysis, or using mixed quantitative/qualita ive methodology

( ) Study involving qualitative meth only

( ) Study limited to working with human sue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data specific project only)

( ) Research tissu ank

( ) Research database

If your work does not fit any o these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (•) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(•) No
b) Will you be taking new human tissue samples (or other human biological samples)?	(•) Yes	( ) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(•) No

DRAFT

d) Will the study involve any other clinical procedures with participants (e.g. MRI, ultrasound, physical examination)? (●) Yes ( ) No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

- [x] England
- [ ] Scotland
- [ ] Wales
- [ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (●) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which applications do you require?

IMPORTANT: If your project is taking place in the NHS and is led from Eng d select 'IRAS Form'. If your project is led from Northern Ireland, Scotland or Wales select 'NHS SC Research and De opment Offices' and/or relevant Research Ethics Committee applications, as appropria e.

- [x] IRAS Form
- [ ] Confiden iality Advisory Group (CAG)
- [ ] National Offender Management Service (MS) (Prisons & Probation)

For NHS/HSC R&D Offices in North Irel tland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in a d tion to the s udy wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisatio in Engl different arrangements apply for the provision of site specific information. Refe to IRAS Help fo more in ormation.

Most research projects re ire review by a REC within the UK Health Departments' Research Ethics Service. Is your study exempt from REC iew?

( ) Yes (●) No

5. Will any research sites in this study be NHS organisations?

(●) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or a Diagnostic Evidence Co-operative in all study sites?

Please see information button for further details.

( ) Yes (●) No

DRAFT

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

(•) Yes ( ) No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

( ) Yes (•) No

7. Do you plan at any stage of the project to undertake intrusive r arch in olving adults lacking capacity to consent for themselves?

( ) Yes (•) No

Answer Yes if you plan to recruit living participants aged 16 or who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the l ving uiring consent in law. This includes use of identifiable tissue samples or personal information, excep where applic tion is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks fo esearch invo ving adults lacking capacity in the UK.

8. Do you plan to include any particip ts wh isoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the pr ation service in England or Wales?

( ) Yes (•) No

9. Is the study or any par f it being undertaken as an educational project?

(•) Yes ( ) No

Please describe briefly he involvement of the student(s):
Dr Jayasish Ghosh (applicant) will be using this as part of his PhD which will be supervised by Prof A Coomarasamy

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

(•) Yes ( ) No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

( ) Yes (•) No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

DRAFT

○ Yes ◉ No

DRAFT

Integrated Research Application System
Application Form for Basic science study involving procedures with human participants

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
The role of hydrosalpinx in recurrent miscarriage

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

The role of hydrosalpinx in recurrent miscarriage

A2-1. Educational projects

Name and contact details of student(s):

Student 1

	Title Forena /Initials Surname
	Dr J
Address	Academic Unit, 3rd loor, Birmingham Women's Hospital
	Mindelsohn ay
	Edgbaston, Bi ingham
Post Code	B15 2TG
E-mail	
Telephone	
Fax	

Give details of the educational course or degree for which this research is being undertaken:
Name and level of course/ degree:
PhD at Institute of Metabolism and Systems Research

Name of educational establishment:
University of Birmingham

Name and contact details of academic supervisor(s):

Academic supervisor 1

	Title Forename/Initials Surname
	Prof A Coomarasamy
Address	Academic Unit, 3rd Floor, Birmingham Women's Hospital

DRAFT

	Mindelsohn Way
	Edgbaston, Birmingham
Post Code	B15 2TG
E-mail	
Telephone	
Fax	

Academic supervisor 2

	Title	Forename/Initials	Surname
	Dr	I D	Gallos
Address	Academic Unit, 3rd Floor, Birmingham Women's Hospital		
	Mindelsohn Way		
	Edgbaston, Birmingham		
Post Code	B15 2TG		
E-mail			
Telephone			
Fax			

Academic supervisor 3

	Title	Forename/Initials	Surname
	Dr	J J	Chu
Address	Academic Unit, 3rd Floor, Birmingha Women's Hospital		
	Mindelsohn Way		
	Edgbaston, Birmingham		
Post Code	B15 2TG		
E-mail			
Telephone			
Fax			

Please state which academic super or(s) ha responsibility for which student(s):
Please click "Sa ow" before comp ing this table. This will ensure that all of the student and academic supervisor details are shown co ctly.

Student(s)	Academic supervisor(s)
Student 1 Dr J Ghosh	☑ Prof A Coomarasamy ☑ Dr I D Gallos ☑ Dr J J Chu

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

- ○ Student
- ◉ Academic supervisor
- ○ Other

DRAFT

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Prof	A	Coomarasamy
Post	Professor of Gynaecology & Director of Tommy's National Centre for Miscarriage Research		
Qualifications	MBChB, MD, FRCOG		
ORCID ID	0000 0002 3261 9807		
Employer	University of Birmingham		
Work Address	Academic Unit, 3rd Floor, Birmingham Women's Hospital		
	Mindelsohn Way		
	Edgbaston, Birmingham		
Post Code	B15 2TG		
Work E-mail			
* Personal E-mail			
Work Telephone			
* Personal Telephone/Mobile			
Fax			

** This information is optional. It will not be placed in the public domain di closed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator m st be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all corresp nce relating to applications for this project?
This contact will receive copies of all correspondence from REC nd H &D reviewers that is sent to the CI.

	Title	Forenam /Initials	S name
	Dr	Sean	J nnings
Address	Research Support up		
	Room ston Web Building		
	University of B ingham dgbaston, Birmingham		
Post Code	B15 2TT		
E-mail	earchgovernan e@contacts.bham.ac.uk		
Telephone	012 158011		
Fax			

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	
Sponsor's/protocol number:	RG_17-150
Protocol Version:	1.0
Protocol Date:	17/09/2017
Funder's reference number:	
Project website:	

Registry reference number(s):
The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the

DRAFT

International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):
ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number Description	Reference Number
University of Birmingham Research Governance Ref Number	RG_17-150
University of Birmingham Research Support Group Ref Number	ERN_17-1086

A5-2. Is this application linked to a previous study or another current application?

◯ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and rese h information systems, we ask a number of specific questions. This section invites you to give an overview usin nguage comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on th ection.

A6-1. Summary of the study. *Please provide a brief summary e research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where esearch is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be pub shed on the Health Research Authority (HRA) website following the ethical review. Pleas fer to the question specific guidance for this question.*

Attenders at a recurrent miscarriag clinic will e screened f r hydrosalpinges. Miscarriage is defined as spontaneous pregnancy loss befor e fetus eaches viabili y. Hydrosalpinges are an abnormal dilation of a fallopian tube classically caused by sexually tra mitt such as Chlamydia trachomatis, pelvic inflammatory disease, previous abdominal surgery ca ng scar tissue or endometriosis which causes a distal occlusion of the tube. They will be screened by p rming a sterosalpingo-contrast-sonogram (HyCoSy). A HyCoSy is an ultrasound scan performed in the outpatient se g. A ro transvaginal ultrasound scan is performed and then a contrast media is introduce into the uterus via he cerv x and he flow of the contrast through the fallopian tubes is tracked in real time using ultr und. This will en ble me to establish the prevalence of hydrosalpinges in the recurrent miscarriage populatio will then follo up both those who screen positive and those who screen negative for hydrosalpinges for 12 m hs in term of their subsequent pregnancy outcomes. I will compare these 2 cohorts to each other to establish the gnosis of miscarriage in women with concurrent hydrosalpinges. If women are found to have hydrosalpinges they and ir routine healthcare provider will be informed and treated appropriately. This may include surgical treatment. The pregnancy outcomes of hose who were treated with surgery will then be compared to those who did not. This is to see if surgery improves the prognosis of women with recurrent miscarriage and concurrent hydrosalpinges and what type of surgery in particular was better. If the surgery does show an improved prognosis, all those women who initially declined intervention will be re-offered surgery by their routine heal hcare provider.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

Transvaginal pelvic ultrasound scanning is a routine gynaecological investigation for recurrent miscarriage and is usually well tolerated. A Hysterosalpingo-contrast-sonogram (HyCoSy) is a more detailed version of a transvaginal ultrasound scan. It is routinely performed by fertility specialists during investigation for subfer ility to look at tubal

pathology as opposed to recurrent miscarriage which is being investigated here but is also usually well tolerated. A HyCoSy gives more information about tubal patency as it involves he passage of a contrast media via the cervix, through the uterus, into the fallopian tubes and if they are patent, into the peritoneal cavity which will highlight any tubal pathology. Patients will therefore be informed that a transvaginal ultrasound scan is a routine investigation for recurrent miscarriage and that a HyCoSy is a more detailed version of a transvaginal ultrasound scan which involves a vaginal ultrasound probe like a transvaginal ultrasound and uterine instrumentation to allow introduction of the contrast media. The HyCoSy should take approximately 10-15 minutes more than a routine transvaginal ultrasound scan. Patients will have the result of the HyCoSy discussed with hem.

As a HyCoSy involves the passage of a contrast media from he cervix into the uterus and out of the fallopian tubes into the abdominal cavity there is a risk of transmitting infection from the lower genital tract upwards causing pelvic inflammatory disease. This risk will be negated by screening all patients for infection prior to performing the scan and treating with antibiotics if any are present. Patients will be informed of these results of the genital infection screening. Patients will also have a urine pregnancy test performed on the day, just before the HyCoSy to eliminate the risk that a patient maybe unknowingly pregnant.

Patients if they do opt for recruitment, will not be required to attend any more appointments than they usually would beyond heir routine care. Venepuncture and swabs can be taken at recruitment and the subsequent appointment would be for the HyCoSy which would otherwise be a routine transvaginal ultra o d scan. Patients will usually have venepuncture at their first clinic appointment to test for anticardiolipin antibod es an upus anticoagulant anyway and so I believe it would be acceptable to have a further 10mls of blood taken he same e. The taking of swabs to check for genital infection is also routine in gynaecological practice and so I feel most w en would also find this acceptable. I believe most women would find a second appointment acceptable as they wou expect to attend a second appointment for an investigation with most outpatient clini s. The second appointmen would also only be 10-15 minutes longer than for a routine transvaginal ultrasound scan. e follow up would be completed via a telephone consultation or email correspondence which is also the most convenie ption for the patient. Should patients have a hydrosalpinx and need treatment by heir routine healthcare provider, the would need a further appointment to discuss the result of the HyCoSy and consent and plan for this treatment. However, ollow up appointment to discuss the result of the scan would be the usual practice anyway future treatment inc ng surgery, would be part of he routine care provided as decided by the usual healthca e pr in conjunction with the patient, so would not inconvenience the patient any more than usual.

It is important to note hat the recruiter is not part of the rou ne healthcare team providing care and treating patients. All decisions regarding treatment of hydrosalpi s will be ma e by the routine healthcare provider so there will be no pressure on the patient to have treatment of an hydrosalpin es that are found. Therefore there is no ethical dilemma for the recruiter.

In addi ion if any abnormalities are found n the HyCoSy that require immediate treatment hey will be referred to the on-call gynaecology team gham W men's Hospital so as not to delay any potential urgent treatment.

3. PURPOSE AND SIGN OF THE RES ARCH

A7. Select the appropriate ethodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note re iew
- ☐ Case control
- ☑ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observa ion study
- ☐ Randomised controlled trial

☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

What is the prevalence of hydrosalpinges in the recurrent miscarriage population and what is the prognosis of women with recurrent miscarriage and concurrent hydrosalpinges?

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

Explore the role of tubal surgery for improving reproductive outcomes in women with recurrent miscarriage population and hydrosalpinges.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Miscarriage is a very common early pregnancy complication. One in every five pr nancies ends in miscarriage. Recurrent miscarriage is a particularly distressing condition which can affect 1% of uples trying to conceive. According to the Royal College of Obstetricians and Gynaecologists, Gree Top Guide on The Investigation and Treatment of Couples with Recurrent First trimester and Second-trimester Miscarriage, d pite detailed investigation a significant proportion of women with recurrent miscarriage will be labelled as unexplained r urrent miscarriage. Therefore miscarriage is a common problem and it is still not kno n why man women suffer from recurrent miscarriage.

Chlamydia trachomatis is the most common sexually transmitted diseas the UK. Infection with C.trachomatis can cause pelvic inflammatory disease and lead to fallopian tube damage and tal tubal occlusion resulting in hydrosalpinges. Hydrosalpinges can also be caused revious abdominal gery causing adhesions and scar tissue, as well as endometriosis. The prevalence of hydros es in the the recurrent miscarriage population is unknown.

It is well established in literature that hydrosalpinx negative y affects assisted conception outcomes with reduced live birth rates and higher miscarriage rates. And o it is recommended by the National Institute of Care Excellence in their clinical guideline 156 that where they are found they are rem ved, preferably laparoscopically, as this will improve the chances of a live birth. However, recurren miscarriage it s not a problem for the women to fall pregnant and salpingectomy (fallopian tube remova would tly remove any chance of a natural conception forcing women to undergo assisted conception in the fo of in-vitro fertilisation (IVF) which can be financially prohibitive.

The key justification therefore is tha t is not k wn what the relationship between hydrosalpinges and recurrent miscarriage is. It stands to reason tha f C. tra homatis is such a common infection especially amongst young fertile women who mayb ying to conceive, ydrosalpinges as a sequelae of the infection, could also be highly prevalent. As recurrent miscarri is such a dis essing condition and many patients are unfortunately labeled as unexplained recurrent miscarriage it ssential we try to establish other risk factors for the condition. Hydrosalpinges clearly cause increased rates of m carriage with assisted conception and so it would be prudent to establish if hydrosalpinges are prevalen the recurrent miscarriage population and whether their presence is associated with an increased risk of miscarriage i.e. is the prognosis worse for women with recurrent miscarriage and concurrent hydrosalpinges? It is also not known whether treatment of hydrosalpinges in the form of surgery, is of any benefit in terms of reducing the risk of miscarriage. If it is found that hydrosalpinges are highly prevalent in the recurrent miscarriage population and that their presence results in a poorer prognosis regarding future pregnancies then we can start to give some answers to women who may previously have been labelled as unexplained recurrent miscarriage. And further to this, if surgery is shown to reduce the risk of miscarriage we maybe able to offer some of these devastated patients a potential treatment.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

This is an observational cohort study primarily aiming to establish the prevalence of hydrosalpinges in the recurrent miscarriage population and the prognosis of women with recurrent miscarriage and concurrent hydrosalpinges.

Population to be studied
Participants will be approached at the Tommy's recurrent miscarriage clinic held at the Birmingham Women's Hospital.

Inclusion criteria include
• Age 18-45
• Diagnosis of recurrent miscarriage
• Ability to give informed consent
Such a wide inclusion criteria will enable a true assessment of the prevalence of hydrosalpinges in the recurrent miscarriage population.

Identifying Participants
All women presenting to the clinic will be screened for eligibility by the routine healthcare provider.
They will then be approached by Dr Jayasish Ghosh or one of the members of the research team. Patients will be offered the patient information leaflet and offered recruitment into the study.

Length of time of recruitment and target sample size.
203 patients will be recruited over 48 months and then subsequen ly followed up for 12 months. Allowing for a 10% level of attrition, it is estimated 184 patients would be required to reach significant results hence 203 patients as a target.

Data to be collected
Titres of IgA and IgG against Chlamydia trachomatis.
Genital infection screen – This is required as per na ional guidance prior to any ute e instrumentation to reduce the risk of subsequent pelvic inflammatory disease during Hysterosalpingo-c rast-sonog phy.
To establish the first objective of prevalence, recruited patients will be screened wi h a Hy erosalpingo-contrast-sonogram (HyCoSy) for the presence or absence of hydrosalpinges

Outcomes to be collected
To establish the second objective of prognosis of women with recurre miscarriage and concurrent hydrosalpinges, pregnancy outcome data will be collected from both cohorts of patients (tients who screen positive and those who screen negative for hydrosalpinges. Specifically this will include:
1) Biochemical pregnancy – a positive pregnancy tes er on urine or serum egnancy testing before ultrasound evidence of a gestational sac
2) Clinical pregnancy – a pregnancy confirmed by evide ce of a e artbeat on ultrasound scan or using ultrasound parameters (ultrasound visualization of a gestational sac embryonic po e with heartbeat).
3) Pregnancy loss and at what gestation the pregnancy wa lost – if unfortunately the patient suffered from a further miscarriage or stillbirth, the gestation in wee of the loss will be noted
4) Ectopic pregnancy – if a clinical pregnancy seen on ultr sound scan but its location of implantation has taken place outside the uterine cavity, t s known as an ectopic p egnancy. Ectopic pregnancies are usually inside the fallopian tube although rarely they can e ab rian or cervical.
5) Live births and obstetric outcomes – i rtunately a patient has a live birth, the gesta ion of birth in weeks, birth weight and neonatal rates ion will b oted.
To explore the role of tubal surgery e same gnancy outcomes listed above will be collected for the cohort of patients that were t eated with surger or their hydrosalpinges.

Reason for choice of CoSy over alte natives
Hysterosalpingo-contras onography (HyCoSy) has been chosen as the screening method as it offers the best compromise from he optio available. It offers comparable levels of sensitivity and specificity for he detection of hydrosalpinges to Hysterosal gography (HSG) whilst not using ionising radiation and possibly an iodine based contrast dye unlike a HSG. It a so requires less specialist equipment as it is not performed in a radiology department with an X-ray machine. And on comparison to a diagnostic laparoscopy and dye test, it is significantly safer and cheaper than an operation requiring a general anaesthetic and physical entry into the abdominal cavity.

Method of Collec ion of data
The genital infection screen will be performed by taking vaginal swabs after written informed consent has been gained.
IgG and IgA titres against Chlamydia trachoma is will be collected via venepuncture after written informed consent has been gained.
The presence or absence of hydrosalpinges will be noted at HyCoSy which will be performed after recruitment and written informed consent. A urine pregnancy test will also be performed prior to the HyCoSy to ensure the patient is not unknowingly already pregnant.
The pregnancy outcome data listed above will be collected via a telephone consultation or email consultation conducted at 6 months and 12 months either post HyCoSy or post surgery/ treatment for hydrosalpinges. Should the patient not recall all of the information needed, I will gain her consent to examine her hospital patient records. Should the patient have had treatment at a different hospital trust I will gain her consent to collect the specific information needed directly from that particular hospital's patient records. I will also gain consent to look at her baby's healthcare records should her recall of neonatal events not be complete.

DRAFT

Consent to participation and feedback of result
The conduct of this study will be in accordance with the principles of Good Clinical Practice. All potential participants will be offered a patient information leaflet as well as a copy of the consent form. Participants will be made aware that they can withdraw from the trial at any stage and anonymised information already collected about them up to the stage of withdrawal may be used in the final analysis.
Patients will be informed of the results of their genital infection screen and appropriate treatment will be provided as necessary as per Birmingham Women's Hospital antimicrobial prescribing guidelines.
Patients will also be informed of the results of their titres of IgG and IgA against Chlamydia trachomatis if requested.
Patients will be immediately informed if their pregnancy test performed prior to HyCoSy is posi ive as they will no longer be able to take part in the study.
HyCoSy findings will be shared with the participants immediately. Any HyCoSy findings that may require urgent gynaecological attention will be referred to the on call gynaecology team at the Birmingham Women's Hospital with the patient's consent. Any other ultrasound findings that require non urgent follow up, will be shared with the GP and routine healthcare provider, with the patient's consent.
The results of the study comparing outcomes between patients who were treated with surgery versus those who were not will be distributed to all study participants and those who were not treated surgically will be offered surgery after the conclusion of the study if this is deemed appropriate by their routine healthcare provider.

Data Management
The blood results and ultrasound records will be kept in locked surrounding at all es at the Birmingham Women's Hospital NHS Foundation Trust. A separate log will be kept which connec the patien dentifiable data with the study allocation number and this will be destroyed at the end of the study period. Information w be collected on secured computers and all research team members will have had prior training in Good Clinical Pra e

A14-1. In which aspects of the research process have you actively in lved, or will you involve, patients, service users, and/or their carers, or members of the public?

- ☐ Design of the research
- ☐ Management of the research
- ☐ Undertaking the research
- ☐ Analysis of results
- ☑ Dissemination of findings
- ☐ None of the above

Give details of involvement, or if n e please stify the absence of involvement.
Patients will be informed of the findin of the evalence and prognostic aspects of the study. They will also be informed of whe surgery for hydro lpinges, whatever that maybe, reduces the risk of further miscarriage. However, it is noted t as small num ers of participants are expected, highly significant conclusions may not be able to be drawn from particular s udy. However, it may show that a larger higher powered trial would be feasible.

4. RISKS AND ETHICAL ISSUE

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- ☐ Blood
- ☐ Cancer
- ☐ Cardiovascular
- ☐ Congenital Disorders
- ☐ Dementias and Neurodegenerative Diseases
- ☐ Diabetes

DRAFT

- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [x] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Heal h
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [x] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Female pa icipants only
Lower age limit: 18	Years
Upper age limit: 45	Years

A17-1. Please list the principal inclusion crite a (list the most important, max 5000 characters).

Female
Age 18-45
Diagnosis of recurrent m carr
Ability to give informed consent

A17-2. Please list the princ l exclusion criteria (list the most important, max 5000 characters).

Allergy to contrast media used or Hysterosalpingo-contrast-sonogram
Allergy to sonographic gel used for ultrasound scanning
Anatomical anomaly meaning transvaginal ultrasound scan not possible
Stenosed/occluded cervix meaning contrast media unable to be introduced via cervix
Inability to give informed consent
Pregnant at the time of recruitment
Declined recruitment

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If his intervention/procedure would be routinely given to participants as part of their care outside the research,

DRAFT

how many of the total would be routine?

3. Average ime taken per interven ion/procedure (minutes, hours or days)

4. Details of who will conduct he intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Consent for recruitment into study	1	0	30 minutes	Dr Jayasish Ghosh (Clinical Research Fellow) in outpatients at Birmingham Women's Hospital
Follow up telephone consultation/email at 6 months	1	0	10 minutes	Dr Jayasish Ghosh (Clinical Research Fellow)
Follow up telephone consultation/email at 12 months	1	0	10 minutes	Dr Jayasish Ghosh (Clinical Research Fellow)

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological mate al. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part o he research protocol.

2. If his intervention/procedure would be routinely given to pa ipants as part of their care outside the research, how many of the total would be routine?

3. Average time taken per intervention/procedure (minutes, hours or ys).

4. Details of who will conduct he intervention/pr cedure, and where it take place.

Intervention or procedure	1	2	3	4
Genital infection screen via vaginal swabs	1	1	10 minutes	Dr Jayasish Ghosh (Clinical Research Fellow) in Outpatients at Birmingham Women's Hospital
Venepuncture for IgG and IgA titre against Chlamydia trachomatis	1	0	10 minutes	Jayasish Ghosh (Clinical Research Fellow) in Outpatients at Birmingham Women's Hospital
Hysterosalpingo-contrast-sonogram to screen for Hydrosalping s	1	0	45 minutes	Dr Jayasish Ghosh (Clinical Research Fellow) in the Birmingham Women's Early Pregnancy Unit

A21. How long do you ect each par cipant to be in the study in total?

Approximately 13-14 month fter recruitment if the patient screens negative for a hydrosalpinx or screens positive but is not treated by their usual he hcare provider in the form of surgery as follow up will be for 12 months after the Hysterosalpingo-contrast sonogram.
If the patient screens positive for a hydrosalpinx and is treated with surgery, it may take 14-15 months due to practically finding a mutually acceptable date for the operation and hen subsequently following them up for 12 months after the operation has been performed.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

There is the time burden. Patients will have a recruitment and consent interview taking 30 minutes followed by genital infection screening and venepuncture which should take less than 10 minutes each. They will also have Hysterosalpingo-contrast-sonography (HyCoSy) which may take 45 mins. The follow up pregnancy outcome data will be collected via telephone consultations or email to minimise the time burden to patients and should not last longer than 10 minutes. Patients will also be made aware of the time commitment during recruitment and consent.

There is the emotional burden and distress that maybe caused by collecting the pregnancy outcome data at 6 and 12 months. As data may be collected on further miscarriages, stillbirths and other distressing events it is conceivable

DRAFT

patients maybe upset by recalling such events. Patients will have been warned about the nature of the data collection at consenting. There is a specific section in the consent form for participation in the study about the potential sensi ive nature of the data that will be collected in the future. They will also be interviewed about the events in a sensitive appropriate manner by a healthcare professional who has been trained and has experience of communication during sensitive and difficult situations.

There is a burden of having a genital infection screen, however, this is also very routine and usually very well tolerated.
There is the burden of having venepuncture, however, this is only on one occurrence and venepuncture is also part of the routine investigations for recurrent miscarriage. A small additional volume of blood would be needed which would be less than 10mls which can be collected at the same time as other routine recurrent miscarriage investigation blood tests.

There is a small risk of allergic or adverse reaction to the contrast media used in Hysterosalpingo-contrast-sonography (HyCoSy). Risk will be minimised by enquiring of any known allergies. The absolute risk of a reaction to the contrast media or the sonographic gel is minimal as they are inert substances that are specifically designed for the task.

There is the discomfort of a transvaginal ultrasound scan and passage of the co ast media which patients will be warned about. However, this is usually minimal and such an investigation is very r ne and well tolerated in usual gynaecological practice for example during a Hysterosalpingogram (HSG) which is ve similar in terms of the passage of the contrast media or a transvaginal ultrasound scan which is the usual inve gation for recurrent miscarriage.

A24. What is the potential for benefit to research participants?

They will get genital infection screening and appropriate treatment, which w ld not usually be carried out.
They will get a more detailed transvaginal ultrasound in the form of a Hy osalpingo-contrast-sonogram giving more details about tubal patency and pelvic anatomy.
They may avoid the ionising radiation of a Hysterosalpingogram
They will be contributing towards the medical knowledge surr unding r current miscarriage which they themselves are afflicted by which could help to improve their own care the future.

RECRUITMENT AND INFORMED C SENT

In this section we ask you to describe th recruitment procedures for the study. Please give separate details for different study group where ap priate.

A27-1. How will po tial participants, ecords or samples be identified? Who will carry this out and what resources will be used?*For exam identification may involve a disease register, computerised search of social care or GP records, or review of medical recor Indicate whether this will be done by the direct care team or by researchers acting under arrangements with the respo ible care organisation(s).*

Women or couples attempting o conceive will likely attend their registered GP practice after having suffered 2 or more miscarriages with concerns about their inability to have a child. The patients will then be referred by their primary care physician to the recurrent miscarriage clinic held at Birmingham Women's Hospital.

Patient's may also be referred to the recurrent miscarriage clinic from the Birmingham Women's Hospital early pregnancy assessment unit (EPAU) during treatment for a miscarriage or from the gynaecology ward also during treatment for a miscarriage.

All women presenting to the recurrent miscarriage clinic held at Birmingham Women's Hospital will be screened for the inclusion criteria by the routine healthcare provider who is holding the clinic. They will be consented for a discussion with Dr Jayasish Ghosh (Clinical Research Fellow) or a designated member of the research team about the study or to have heir contact details passed along as they have met the eligibility criteria for the study. Dr Jayasish Ghosh has an honorary contract with Birmingham Women's Hospital to allow him to carry out clinical care. Other members of the research team also have contracts with Birmingham Women's Hospital to allow them to carry out clinical work.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

DRAFT

◉ Yes ○ No

Please give details below:
All women presenting to the clinic will be screened for he inclusion criteria by the routine healthcare provider. The routine healthcare provider will then consent the patient to a discussion with Dr Jayasish Ghosh (Clinical Research Fellow) or a designated member of the research team about the study and potential recruitment. Dr Ghosh or a member of the research team will not be reviewing or screening potential recruits.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

When a patient is identified by the routine healthcare provider in the recurrent miscarriage clinic as fitting the inclusion criteria they will be consented to having their details discussed with Dr Jayasish Ghosh (Clinical Research Fellow) or a designated member of the research team. If the patient does not consent to thi or does not want to discuss the study with the research team then no details of the patient will be passed onto Dr yasish Ghosh or any members of the research team. This will ensure that no patient identifiable information i known b any member of the research team unless consent has been gained by the routine healthcare provider the eby ensur no breach of the duty of confidentiality.

In addition all patient information stored electronically will be sto on secure servers inside the Birmingham Women's Hospital firewall or the University of Birmingham firewall a phy ical information will be kept in secure, locked conditions at Birmingham Women's Hospital. All staff accessing atient information will have had appropriate information governance training by Birmingham Women's Hospital. No pa nt identifiable data will be transferred under any circumstances. In addition all members of he research team will Good Clinical Practice (GCP) trained and information governance trained.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

◉ Yes ○ No

A27-5. Has prior consent been ob ned or it be obtained for access to identifiable personal information?

◉ Yes ○ N

If Yes, please give deta below.
As the main data collection ill be performed at 6 months and 12 months after recruitment it is conceivable patients will be asked about specific e ts and information which occurred several months prior. Their recall may not be complete and so on the consent for recruitment onto the study there will be a section designated to gaining written informed consent to access the patient's hospital records to complete data collection should this be required. It is also conceivable that as there are several other hospitals locally who can provide early pregnancy and obstetric care, the required information maybe at other trusts. And so patient's will also be consented on the study recruitment consent form to obtain this information from hospital records at other hospitals.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

If the potential participant consents to a discussion about the study by the routine healthcare provider they will be approached by Dr Jayasish Ghosh (Clinical Research Fellow) or a designated member of the research team. All members of the research team are GCP trained. The approach will be at the patient's convenience. It maybe after the consultation with the routine healthcare provider, or at a subsequent appointment depending upon patient choice. Dr

Jayasish Ghosh is a clinical gynaecology registrar who holds an honorary contract with Birmingham Women's Hospital allowing him to carry out clinical work.

A30-1. Will you obtain informed consent from or on behalf of research participants?

(•) Yes ( ) No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Consent will be taken by Dr Jayasish Ghosh (Clinical Research Fellow) or a designated member of the research team. Patients will have been given a patient information leaflet prior to their appointm nt with their appointment letter. At the appointment they will have a discussion about he study allowing them to ask any questions they have about the study, what they are required to do, their ime commitments and length of follow up. Consent will be taken via a written consent form which is attached. They are also free to discontinue with e trial at any time without having to give a reason. Pa ients will also be given a dedicated study phone numb r to they n contact Dr Jayasish Ghosh at their convenience to ask further questions. Consent will only be sought fr m compete adults with capacity to consent.

If you are not obtaining consent, please explain why not.

NA

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consu tee writing?

(•) Yes ( ) No

A31. How long will you allow potentia artic t d cide whether or not to take part?

Patients will be given the p formati eaflet at the same time as their appointment letter for the recurrent miscarriage clinic thus allowing su ient tim r them to read the leaflet before being consented for recruitment. Patients will have the ability to consen on the d y when they are first physically approached about the study if they choose to. Should y require some a ditional time to decide on whether to participate they will be allowed until the target number for rec tment is met. P ients will also be informed that they have the right to decide to not continue with their participation in e study at a y time they choose. They would not have to give a reason for their choice and their care would not be affe d.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

(•) Yes

( ) No

( ) Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Patient's attending he recurrent miscarriage clinic may also be consented to be entered onto Tommy's net which captures demographic and clinical data for epidemiological research. This would not affect the results for this study. Known confounders for example due to involvement in interventional studies will be adjusted for during statistical analysis for the prognosis element of the study. Involvement in other studies would also not affect the results of the prevalence study.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

DRAFT

Use of a telephone based interpretation service is freely available in the department where the appointments will be carried out.
Use of sign language interpreters, if needed, will be organised on an ad hoc basis.
If satisfactory consent can not be obtained for whatever reason, then the patient will be excluded from the study.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ◉ The par icipant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ○ The participant would continue to be included in the study.
- ○ Not applicable – informed consent will not be sought from any participants i this research.
- ○ Not applicable – it is not practicable for the research team to monitor capacity a con inued capacity will be assumed.

Further details:

Should a patient lose capacity they would not longer be able to part ate in the prognostic and intervention parts of the study and so hey would be withdrawn from this part of the study. Howe their participation in the prevalence part would already be complete so this would not be affected.

If you plan to retain and make further use of identifiable d issue following lo s of capacity, you should inform participants about this when seeking their consent initia ly.

CONFIDENTIALITY

In this section, personal data mea any dat relating to a participant who could potentially be identified. It includes pseudonymised data capable of bein nk pant through a unique code number.

Storage and use of personal data ring th tudy

A36. Will you be u ertaking any of th following activities at any stage (including in the identification of potential participants)? *(Tick appropriate)*

- ☑ Access to medical re ds by th se outside the direct healthcare team
- ☐ Access to social care rec by those outside the direct social care team
- ☑ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☑ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files (includes paper or film)
  - ☑ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers

DRAFT

- [x] University computers
- [ ] Private company computers
- [ ] Laptop computers

Further details:
Blood test results, swab results, ultrasound reports, operative reports are all held on secure information systems at Birmingham Women's Hospital.
Consent will be sought to access these and the medical notes of participants at the time of recruitment. This maybe needed as patients may have imperfect recall about events which occurred several months prior to data collection which will occur at 6 and 12 months after recruitment.
Personal contact information will be needed to contact patients for their 6 and 12 month follow up telephone consultations or email consultations. And also to distribute the results of the study at its conclusion and to contact patients who were not treated surgically to see if they would like to re-discuss surgery with their routine healthcare provider if it has been shown to significantly improve pregnancy outcomes.
Physical trial documents will also be kept as a backup to help collate and collect all relevant data. These will be stored in the same manner as any patient medical records in locked secured surround s at Birmingham Women's Hospital.

A37. Please describe the physical security arrangements for storage of personal data du g the study?

The blood results, swab results, ultrasound records, operative rec s and p egnancy outcome data will be kept in locked surroundings at all times at the Birmingham Women's Hospit NHS Foundation Trust or on secure trust information systems and computers.
Personal contact information will also be stored on the Lorenzo Patient Inf ation system which is a secure purpose designed information system at Birmingham Women Hospital.

A38. How will you ensure the confidentiality of personal data?*Please vide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation o pseudonymisation of data.*

The blood results, swab results, ultrasound re ords, operati e records and pregnancy outcome data will be kept in locked surroundings at all times a he Birmingham Women's Hospital NHS Foundation Trust or on secure trust information systems and computers separa e log will be kept which connects the patient identifiable data with the study allocation number and this will b estroyed end of the study period. Information will be collected on secured computers and all research team embers will have had prior training in Good Clinical Practice. Only non patient identifiable data will be al ed to be hared outside of the Birmingham Women's Hospital.

A40. Who will have ess to participa ts' personal data during the study? *Where access is by individuals outside the direct care team, please stify and say whether consent will be sought.*

Dr Jayasish Ghosh (clinical search fellow) and other designated members of the research team. This may include Dr Ioannis Gallos who is an H rary Academic Clinical Lecturer and sub-speciality trainee in reproductive medicine and surgery at Birmingham Women's Hospital. As well as Dr Justin Chu who is an Academic Clinical Lecturer and registrar in obstetrics and gynaecology also at Birmingham Women's Hospital. All 3 are GCP trained.
Consent will be sought at trial recruitment for Dr Jayasish Ghosh to have access to patient's medical records and personal data. This access will be required to ensure complete and thorough data collection if the patient's recall is imperfect.
The patient's direct care team will also have access as is usual practice in clinical care.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

It will be analysed and stored on secure computers at Birmingham Women's Hospital in the academic department. It will be analysed by Dr Jayasish Ghosh. Non patient identifiable data may need external statistical analysis. Under no circumstances will the study data seen by an external statis ician have any patient iden ifiable information.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Mrs	Kelly	Hard
Post	R&D Manager at Birmingham Women's Hospital		
Qualifications			
Work Address	R&D Office		
	Birmingham Women's Hospital		
	Mindelsohn Way, Edgbaston, Birmingham		
Post Code	B15 2TG		
Work Email			
Work Telephone			
Fax			

A43. How long will personal data be stored or accessed after the study has ende

- ○ Less than 3 months
- ○ 3 – 6 months
- ◉ 6 – 12 months
- ○ 12 months – 3 years
- ○ Over 3 years

A44. For how long will you store research data generated by the study?

Years: 10
Months:

A45. Please give details of the lo term ar gements for storage of research data after the study has ended. *Say where data will be stored, who will ha access d the arrangements to ensure security.*

Data will be stored ecure locked de ignated room at Birmingham Women's Hospital. Once finished the data will be incinerated. Only m bers of the o ginal study team will be allowed access. All results, records and data will be managed in line with the a Protection Act, 1998.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may

DRAFT

give rise to a possible conflict of interest?

◯ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◉ Yes ◯ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

◉ Yes ◯ No

It should be made clear in the participant's information sheet if the GP/health professional ll be informed.

PUBLICATION AND DISSEMINATION

A50-1. Will the research be registered on a public database?

The Department of Health's Research Governance Fr m rk for Health and ocial Care and the research governance frameworks for Wales, Scotland and Northern Irela et out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Decla ation elsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Jou ditors (ICMJE will consider a clinical trial for publication only if it has been registered in an appropriate registry. Pl se see guidance for more information.

◉ Yes ◯ No

Please give details, or justify if not registe g the research.
It will be registered at https://ww linicaltri gov/ - the website for Clinicaltrials.gov - a registry and results database of publicly and privately supported ical stu of human participants conducted around the world.

Please ensure that u have entered r gistry reference number(s) in question A5-1.

A51. How do you intend to re rt and disseminate the results of the study? *Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☑ Internal report
- ☑ Conference presentation
- ☑ Publication on website
- ☑ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

When results are published the individual data will have been collated into cohorts and anonymised so there is no risk of a breach of confidentiality or anonymity. No patient identifiable data will be published.

A53. Will you inform participants of the results?

(•) Yes ( ) No

Please give details of how you will inform participants or justify if not doing so.
Email addresses will be collected when patients are first consented and recruited into the trial. The results of the study including, prevalence, prognosis and whether surgery improves the prognosis of women with recurrent miscarriage and concurrent hydrosalpinges will be distributed via an email newsletter to all participants at the conclusion of the study if they provide an email address. The email address of the participants will be destroyed after this.

5. Scientific and Statistical Review

A54-1. How has the scientific quality of the research been assessed? *Tick as ap opriate:*

- [ ] Independent external review
- [ ] Review within a company
- [ ] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisa
- [ ] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If th review has been undertaken but not seen by the researcher, give details of the body which ha undertaken the review:
The research proposal was formally reviewed Prof T J Cla k - Consultant Obstetrician and Gynaecologist from the College of Medical and Dental St s at the University of Birmingham. It was graded at level 3 which means "Very Good: You would recommend that th Medic l should accept the application for submission to the specified programme".

For all studies except non-doctoral dent res rch, please enclose a copy of any available scientific critique reports, together with any related corresponde e.

For non-doctoral stud research, plea e enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistica spects of the research been reviewed? *Tick as appropriate:*

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company sta is ician
- [ ] Review by a statis ician wi hin the Chief Investigator's institution
- [x] Review by a statistician wi hin the research team or multi−centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

DRAFT

	Ti le	Forename/Initials	Surname
	Dr	Aurelio	Tobias
Department	Institute of Metabolism and Systems Research		
Institution	University of Birmingham		
Work Address	Academic Unit, 3rd Floor, Birmingham Women's Hospital		
	Mindelsohn Way		
	Edgbaston, Birmingham		
Post Code	B15 2TG		
Telephone			
Fax			
Mobile			
E-mail			

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

The prevalence of hydrosalpinges in the recurrent miscarriage population and the progn s of patients with recurrent miscarriage and concurrent hydrosalpinges.

A58. What are the secondary outcome measures?*(if any)*

Is the prognosis of women with recurrent miscarriage and concurrent hydr alpinges improved by surgical intervention.

A59. What is the sample size for the research? *How many pa ticipan amples/data records do you plan to study in total? If there is more than one group, please give further det ils below.*

Total UK sample size: 203
Total international sample size (i ding UK) 203
Total in European Economic Area:

Further details:

A60. How was the s ple size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient informa n to justify an reproduce the calculation.*

For a prevalence study in a ndition where the prevalence is unknown but not expected to be higher than 25% for obtaining a 95% level of confi ce and precision at 0.05 we have estimated that 184 patients are required. To account for up to a 10% level o attrition, approximately 203 patients should be recruited.

A61-1. Will participants be allocated to groups at random?

○ Yes ◉ No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

For the prevalence survey of hydrosalpinx in the recurrent miscarriage population data will be presented using descriptive statistics. We will examine the prevalence data within subgroups created from the results of titres of IgA and IgG against C. trachomatis and clinical characteristics for example age, body mass index, previous sexually transmitted infections to identify high risk groups for hydrosalpinx.

For the comparison of the cohorts we will report numbers of individuals at each stage of study e.g. numbers potentially

DRAFT

eligible, examined for eligibility, confirmed eligible, included in he study, completing follow-up, and analysed. The reasons for non-participation at each stage will be described. We will also describe the characteristics of study participants (e.g. demographic, clinical) as well as the information regarding their results of titres of IgA and IgG against C. trachomatis and potential confounders (e.g. age, body mass index.) We will indicate the number of participants with missing data for each variable of interest and compute data for missing covariates using maximum likelihood estimation. We will summarise follow-up time (e.g. average and total amount) and report numbers of outcome events over ime for each cohort. We will report unadjusted relative risk estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. at the 95% confidence interval). We will endeavour to translate estimates of relative risk into absolute risk for a meaningful time period. Subgroup analyses will be also performed according to the risk stratification described above.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers*

	Title	Forename/Initials	Surname
	Dr	J	Ghosh
Post	Clinical Research Fellow/ Registrar in Obstetr cs and Gynaecology		
Qualifications	MBBS, BSc		
Employer	Tommy's National Centre for Miscarriage Resear nstitute of Metabolism and Systems Research, University of Birmingham		
Work Address	Academic Unit, 3rd Floor,		
	Birmingham Women's Hospital, Mind hn Way		
	Edgbaston, Birmingham		
Post Code	B15 2TG		
Telephone	0121 623 6837		
Fax			
Mobile			
Work Email			

	Title	Forename tials	S name
	Dr	J J	Chu
Post	ademic Clinical Lecturer/ Registrar in Obstetrics and Gynaecology		
Qualifications	MB B MRCOG, PhD		
Employer	Univers of Birmingham, Institute of Metabolism and Systems Research		
Work Address	Academic Unit, 3rd Floor		
	Birmingham Women's Hospital, Mindelsohn Way		
	Edgbaston, Birmingham		
Post Code	B15 2TG		
Telephone			
Fax			
Mobile			
Work Email			

	Title	Forename/Initials	Surname
	Dr	I D	Gallos
Post	Honorary Clinical Lecturer/ Sub-specialist trainee in Reproductive Medicine and Surgery		
Qualifications	DMS, MD, MRCOG		
Employer	Birmingham Women's Hospital NHS Foundation Trust		
Work Address	Academic Unit, 3rd Floor,		

DRAFT

	Birmingham Women's Hospital, Mindelsohn Way Edgbaston, Birmingham
Post Code	B15 2TG
Telephone	
Fax	
Mobile	
Work Email	

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

Com ercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	University Birming m
Given name	Sean
Family name	Jennings
Address	esearch Support Group, Room 119, Aston Webb Building
Town/city	Un rsity of Birmingham, Edgbaston
Post code	B15 2
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	researchgovernance@contacts.bham.ac.uk

Is the sponsor based outside the UK?

○ Yes ◉ No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?

DRAFT

☑ Funding secured from one or more funders
☐ External funding application to one or more funders in progress
☐ No application for external funding will be made

What type of research project is this?

○ Standalone project
○ Project that is part of a programme grant
○ Project that is part of a Centre grant
◉ Project that is part of a fellowship/ personal award/ research training award
○ Other

Other – please state:

Please give details of funding applications.

Organisation	Tommy's National Centre for Miscarriage Re arch, Insti te of Metabolism and Systems Research, College of Medical and Dental Scie s,
Address	University of Birmingham, Academic Unit, 3rd Floor Birmingham Women's Hosp Foundation Trust Mindelsohn Way, Edgbaston, Bir ham, West Midland
Post Code	B15 2TG
Telephone	
Fax	
Mobile	
Email	

Funding Application Status: ◉ Secured ○ In progress

Amount: £82 000

Duration
Years: 3
Months:

If applicable, please specify t e programme/ funding stream:

What is the funding stream/ programme for this research project?

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

○ Yes ◉ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

○ Yes ◉ No

DRAFT

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Mrs	Kelly	Hard
Organisation	Birmingham Women's Hospital		
Address	Mindelsohn Way		
	Edgbaston		
	Birmingham		
Post Code	B15 2TG		
Work Email			
Telephone			
Fax			
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Local Clinical Research Network for NHS Organisation i tified in A68-1:

West Midlands

For more information, please refer to the question specific guidance.

A69-1. How long do you expect th tudy to la t in the UK?

Planned start date: 01/02/2018
Planned end date: 31/07/202
Total duration:
Years: 2 Months Days: 31

A70.

Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial

Once 12 month follow up data from the last patient recruited has been collected. This will be approximately 14-15 months after the recruitment period has ended which will allow time to organise any potential treatments and operations performed by the routine healthcare team and then follow them up for 12 months.

A71-1. Is this study?

- (●) Single centre
- ( ) Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- [x] England
- [ ] Scotland

DRAFT

☐ Wales
☐ Northern Ireland
☐ Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?
◯ Yes ◉ No

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England	1
☐ NHS organisations in Wales	
☐ NHS organisations in Scotland	
☐ HSC organisations in Northern Ireland	
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP prac ices in Northern Ireland	
☐ Joint health and social care agencies (eg community mental health teams)	
☐ Local authorities	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent (private or voluntary ctor) organisations	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give deta	

Total UK sites in study: 1

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

◯ Yes ◉ No

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:** in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the

DRAFT

arrangements and provide evidence.

☐ NHS indemnity scheme will apply (NHS sponsors only)

☑ Other insurance or indemnity arrangements will apply (give details below)

The University of Birmingham has in force a Public Liability Policy and/or Clinical Trials Policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed t e research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arra gements and provide evidence.

☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☑ Other insurance or indemnity arrangements will apply (give details below)

The University of Birmingham has in force a Public Liability Policy d/or Clini al Trials Policy which provides cover for claims for "negligent harm" and the activities here are included within at coverage.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ o emnity to meet the potential legal liability of investigators/collaborators arising from harm to partic pants in th duct of the research?

Note: Where the participants are NHS patients indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole udy (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the resea ch, includi g private prac ices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professio indemnity will apply (participants recruited at NHS sites only)

☐ Research include non-NHS s (give tails of insurance/ indemnity arrangements for these sites below)

All research particip ts will be recruite at a NHS site and be covered under NHS indemnity

Please enclose a copy of levant documents.

A78. Could the research lead t the development of a new product/process or the generation of intellectual property?

◯ Yes ◯ No ◉ Not sure

A79. Please select the level of commercial participation in this project.

◉ None

◯ Industry funding, but not industry sponsored

◯ Industry funding and industry sponsored

◯ Industry sponsored, but not industry funded

A80. Please select the main subject area of research. Additional sub-topics may be selected, if required

☐ Age and Ageing

DRAFT

- [ ] Anaesthetics
- [ ] Cancer (includes malignant haematology
- [ ] Cardiovascular
- [ ] Clinical
- [ ] Critical Care
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Dermatology
- [ ] Diabetes
- [ ] Ear, Nose and Throat
- [ ] Gastrointestinal
- [ ] Genetics
- [ ] Health Services Research
- [ ] Hepatology
- [ ] Immunology and Inflammation
- [x] Infectious Disease and Microbiology
- [ ] Injuries and Accidents
- [ ] Medicines for Children (does not include Paediatrics)
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal (Rheumatoid Arthritis is a separa cate)
- [ ] Nervous System Disorders
- [ ] Non-malignant Haematology
- [ ] Ophthalmology
- [ ] Oral and Dental
- [ ] Paediatrics (does not include Medi s for Children)
- [ ] Primary Care
- [ ] Public Health Research
- [ ] Renal
- [x] Reproductive Healt nd Childbirth
- [ ] Respiratory
- [ ] Rheumatoid Arthritis
- [ ] Stroke
- [ ] Surgery
- [ ] Urogenital

DRAFT

Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?

High Vaginal microbiology swabs, self taken vulvovaginal microbiology swabs, human blood samples for testing for IgG and IgA against Chlamydia trachomatis.

2. Who will collect the samples?

The samples will be collected by Dr Jayasish Ghosh MBBS who is a Specialist Registrar in Obstetrics and Gynaecology and is fully GMC registered (7293742) with a license to practice medicine. He also has an honorary contract with Birmingham Women's Hospital to carry out clinical care including such procedures. The self taken swab will be taken by the patient herself.

3. Who will the samples be removed from?

- [x] Living donors
- [ ] The deceased

4. Will informed consent be obtained from living donors for use of the s ples? *Please tick as appropriate*

In this research?

(•) Yes ( ) No

In future research?

(•) Yes ( ) No ( ) Not applicable

6. Will any tissues or cells d for hum n application or to carry out testing for human application in this research?

( ) Yes (•) No

8. Will the samples be store *[Tick as appropriate]*

In fully anonymised form? *(link to donor broken)*

( ) Yes (•) No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*

(•) Yes ( ) No

If Yes, say who will have access to the code and personal information about the donor.

Blood samples and microbiology swabs will be stored in the pathology laboratory at Birmingham Women's Hospital in keeping with current standards and standard operating procedures for the Pathology department.

In a form in which the donor could be identifiable to researchers?

( ) Yes (•) No

9. What types of test or analysis will be carried out on the samples?

DRAFT

The high vaginal and self taken vulvovaginal swabs will undergo microscopy, culture and sensitivities as well as nucleic acid amplification testing, both for the detection of pathogens causing infection in the female genital tract.

The human blood samples will undergo IgA and IgG testing against Chlamydia trachomatis which will indicate acute, chronic or previous infection.

Tests will be carried out by trained Birmingham Women's Hospital pathology staff.

10. Will the research involve the analysis or use of human DNA in the samples?

◯ Yes ◉ No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

◉ Yes ◯ No

12. If so, will arrangements be made to notify the individuals concerned?

◉ Yes ◯ No ◯ Not applicable

If No, please justify. If Yes, say what arrangements will be made d give details of the support or counselling service.

Participants and their GP (with patient consent) will be immediately info ed. Depending on the urgency with which the findings need to be dealt with the appropriate routine healthcare team l be informed. For example should any findings require emergency gynaecological assessm t and treatment, the ngs with patient consent, will be discussed with the on-call team for gynaecological emerg s at Birmingham Women's Hospital.

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

Samples will be stored in the patho ogy labora ories of Birmingham Women's Hospital and only accessible by pathology staff.

14. What will happen to th les at th nd of the research? *Please tick all that apply and give further details.*

☑ Transfer to research tissue bank

(If the bank is in Engl d Wales or N rthern Ireland the institution will require a licence from the Human Tissue Authority to store releva material fo possible further research)

☐ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

☐ Storage by research team as part of a new research tissue bank

(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted)

☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☐ Disposal in accordance with the Human Tissue Authority's Code of Practice

☐ Other

☐ Not yet known

DRAFT

Please give further details of the proposed arrangements:

Any samples that are leftover after the study has ended will be transferred and stored under HTA licence at a local bio-bank facility.

DRAFT

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	(•) NHS site ( ) Non-NHS site		Forename	Aravinthan
			Middle name	
	Country: England		Family name	Coomarasamy
			Ema	
			Qualification (MD...)	MBChB, MD, MRCOG
	Organisation name	BIRMINGHAM WOMEN'S AND CHILDREN'S NHS FOUNDATION TRUST	Country	ITED KINGDOM
	Address	STEELHOUSE LANE		
		BIRMINGHAM WEST MIDLANDS		
	Post Code	B4 6NH		

DRAFT

Appendix 7: Confirmation of West Midlands Edgbaston Research Ethics Committee approval for "The role of hydrosalpinx in recurrent miscarriage"

NHS
Health Research Authority

West Midlands - Edgbaston Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

22 December 2017

Prof A Coomarasamy
Professor of Gynaeco ogy & D rector of Tommy's Nat ona Centre for M scarr age Research
Un vers ty of B rm ngham
Academ c Un t, 3rd F oor, B rm ngham Women's Hosp ta
M nde sohn Way
Edgbaston, B rm ngham
B15 2TG

Dear Prof Coomarasamy

Study Title:	**The role of hydrosalpinx in recurrent miscarriage**
REC reference:	**17/WM/0444**
Protocol number:	**RG_17-150**
IRAS project ID:	**232650**

The Research Eth cs Comm ttee rev ewed the above app cat on at the meet ng he d on 13 December 2017.

Provisional opinion

The Comm ttee wou d be content to g ve a favourab e eth ca op n on of the research, subject to rece v ng a comp ete response to the request for further nformat on set out be ow.

Author ty to consider your response and to confirm the Committee's final opinion has been de egated to the Cha r.

Further information or clarification required

1. P ease create a eaf et w th contact deta s for the n house bereavement and support serv ces.
2. Please reword the instances of 'unfortunately' in the Data Co ect on Form.
3. P ease add the recru tment deta s nto the summary f ow chart.
4. P ease add the future use of samp es as an opt ona po nt to the Consent Form.

5. P ease make the fo ow ng changes to the Part c pant Informat on Sheet:

    a. Add nformat on regard ng the emot ona burden of the study.

    b. Add any potent a pos t ve benef ts.

    c. Add 'insurance' to page four.

    d. Make sure a anguage s n p a n Eng sh and then proofread the document.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact Joanne O'Neil, REC Manager.

When subm tt ng a response to the Comm ttee, the requested nformat on shou d be e ectron ca y subm tted from IRAS. P ease refer to the fo ow ng gu dance for nstruct ons on how to subm t a response to prov s ona op n on e ectron ca y from IRAS: https://www.myresearchpro ect.org.uk/he p/h peth ca rev ew.aspx#After subm t to REC

P ease subm t rev sed documentat on where appropr ate under n ng or otherw se h gh ght ng the changes wh ch have been made and g v ng rev sed vers on numbers and dates. You do not have to make any changes to the REC app cat on form un ess you have been spec f ca y requested to do so by the REC.

The Comm ttee w conf rm the f na eth ca op n on w th n a max mum of 60 days from the date of n t a rece pt of the app cat on, exc ud ng the t me taken by you to respond fu y to the above po nts. A response shou d be subm tted by no ater than 21 January 2018.

Summary of the discussion at the meeting

Ethical issues raised by the Committee in private discussion, together with responses given by the researcher when invited into the meeting

- **<u>Social or scientific value; scientific design and conduct of the study</u>**

  The Comm ttee stated the fo ow up quest onna re seemed qu te daunt ng and cou d be d stress ng. It was quer ed f t cou d be comp eted over the phone rather than by ema .

  The applicants confirmed their preferred method was by telephone if possible if participants wished it could be done by email.

  The Comm ttee quer ed f t wou d be poss b e to do the fo ow up face to face f a part c pant requested t.

  The applicants confirmed it would be possible.

  The Comm ttee asked how the nterpretat on and trans at on serv ce wou d work.

The applicants explained the interpreter would be a remote worker the team have access to who would take part in in a three way conversation via telephone.

The Comm ttee were happy w th th s response.

The Comm ttee quer ed what the t me sca e was for the study to recru t 203 part c pants.

The applicants clarified recruitment would be one to two years and confirmed the centre currently saw roughly four new patients a week and a high rate of take up was expected.

The Comm ttee were happy w th the response.

- **Recruitment arrangements and access to health information, and fair participant selection**

  The Comm ttee asked how potent a part c pants were f rst go ng to be approached about the study and by who.

  The applicants explained patients were referred to the clinical of a national scale and the Participant Information Sheet would be sent out with the appointment letter. On the day of their first appointment the registrar would query if they were interested in joining the study and take consent to be contacted which would lead to a discussion with the researcher and if they wished to be included would be consented on the following clinic appointment.

  The Comm ttee added there was no Consent to Contact Form prov ded and asked f consent was be ng taken verba y.

  The applicants confirmed this was the case.

  The Comm ttee were sat sf ed w th th s response.

- **Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity**

  The Sub Comm ttee asked f the study team wou d be ab e to dea w th any ssues of d stress that occurred over the phone or by ema .

  The applicants confirmed the clinic had in-house bereavement and support services that specialised in miscarriage and post birth deaths.

  The Comm ttee suggested a eaf et cou d be prov ded w th the teams deta s on.

  The applicants agreed.

  The Comm ttee were happy w th the response.

- **Informed consent process and the adequacy and completeness of participant information**

  The Comm ttee stated on the who e the Part c pant Informat on Sheet was c ear and conc se however d d conta n some ngu st c qu rks. The Comm ttee suggested the Informat on Sheet was proofread after be ng rev ewed to check that a anguage was n p a n Eng sh so pat ents wou d be ab e to understand what they read.

  The applicants agreed

  The Comm ttee were happy w th th s response.

  The Comm ttee noted the app cat on made ment on of the emot ona burden of the study however th s nformat on was absent from the Part c pant Informat on Sheet. It was stated the nformat on must be added.

  The applicants agreed

  The Comm ttee were happy w th th s response.

  The Comm ttee stated the future use of samp es must be added as an opt ona po nt n the Consent Form.

  The applicants agreed

  The Comm ttee were happy w th th s response.

  In Pr vate d scussion the Committee added the word 'insurance' appeared to be m ss ng on page four of the Part c pant Informat on Sheet.

  The Comm ttee commented any potent a pos t ve benef ts shou d be added to the Part c pant Informat on Sheet.

- **Suitability of supporting information**

  The Committee stated there were too many instances of 'unfortunately' in the Data Co ect on Form and some shou d be reworded.

  The applicants agreed

  The Comm ttee were happy w th th s response.

- **Other general comments**

  In pr vate d scuss on the Comm ttee stated the summary f ow chart d d not deta recru tment and requested the document be updated.

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

- **Suitability of the applicant and supporting staff**

  The Comm ttee noted the student was not part of the c n ca care team, however wou d not be d rect y approach ng potent a part c pants.

P ease contact the REC Manager f you fee that the above summary s not an accurate ref ect on of the d scuss on at the meet ng.

Documents reviewed

The documents rev ewed at the meet ng were:

Document	*Version*	*Date*
GP/consultant information sheets or letters [GP NFORMAT ON SHEET V1 0 RAS D 232650 The role of hydrosalpinx in recurent miscarriage]	1 0	27 October 2017
RAS Application Form [RAS Form 20112017]		20 November 2017
Letter from funder [funding letter 1]		
Letter from funder [funding letter 2]		
Letter from funder [grant letter]		
Letter from sponsor [Sponsor Confirmation Letter]	1 0	14 November 2017
Non-validated questionnaire [Pregnancy outcome data collection form]	1 0	27 October 2017
Participant consent form [PAT ENT CONSENT FORM v1 0 RAS D 232650 The role of hydrosalpinx in recurrent miscarriage]	1 0	27 October 2017
Participant information sheet (P S) [PAT ENT NFORMAT ON SHEET V1 0 RAS D 232650 The role of hydrosalpinx in recurent miscarriage]	1 0	27 October 2017
Referee's report or other scientific critique report [nternal Peer review form J Ghosh by Prof TJ Clark]	1 0	18 July 2017
Research protocol or project proposal [PROTOCOL V1 0 RAS D 232650 The role of hydrosalpinx in recurent miscarriage]	1 0	27 October 2017
Summary CV for Chief nvestigator (C) [Prof A Coomarasamy 2 page CV]	1 0	17 September 2017
Summary CV for student [Dr J Ghosh 2 page summary CV Oct 2017]	1 0	27 October 2017
Summary CV for supervisor (student research) [Prof A Coomarasamy 2 page summary CV as C and Supervisor]	1 0	01 October 2017
Summary CV for supervisor (student research) [Dr D Gallos 2 page CV August 2017]		17 September 2017
Summary CV for supervisor (student research) [Dr J J Chu CV 2 page summary Sept 2017]		17 September 2017

Membership of the Committee

The members of the Comm ttee who were present at the meet ng are sted on the attached sheet

Statement of compliance

The Comm ttee s const tuted n accordance w th the Governance Arrangements for Research Eth cs Comm ttees and comp es fu y w th the Standard Operat ng Procedures for Research Eth cs Comm ttees n the UK.

17/WM/0444	**Please quote this number on all correspondence**

Yours s ncere y

pp.

Mr Paul Hamilton
Chair

Ema : NRESComm ttee.WestM d ands Edgbaston@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments.*

Copy to: *Dr Sean Jennings*
Mrs Kelly Hard, Birmingham Women's Hospital

West Midlands - Edgbaston Research Ethics Committee

Attendance at Committee meeting on 13 December 2017

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Oladipo Babalola	Relief Pharmacy Manager	Yes	
Dr Hora Ejtehadi	Senior Academic Lecturer	Yes	
Mr Chris Foy	Medical Statistician	Yes	
Mr Paul Hamilton	Parish Administrator	Yes	Chair
Dr Adrian Hamlyn	Consultant Physician & Hepatologist	Yes	
Dr Sarahjane Jones	Senior Research Fellow	Yes	
Dr Nigel Langford	Consultant Clinical Pharmacologist & General Physician	No	
Professor John Marriott	Pharmaceutical Chemist/Academic Pharmacist	Yes	
Mrs Alison Parsons	Retired Senior Manager	Yes	
Mr Philip Russell	Retired Head Teacher	Yes	
Dr Michael Wolffe	Optometrist	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Joanne O'Neil	REC Manager

Appendix 8: Confirmation of NHS Health Research Authority approval for "The role of hydrosalpinx in recurrent miscarriage"

NHS
Health Research Authority

Professor A Coomarasamy
Professor of Gynaecological Research & Director of Tommy's National Centre for Miscarriage Research
University of Birmingham
Academic Unit, 3rd Floor, Birmingham Women's Hospital
Mindelsohn Way
Edgbaston, Birmingham
B15 2TG

Email hra.approval@nhs.net

16 January 2018

Dear Professor Coomarasamy,

Letter of HRA Approval

Study title:	**The role of hydrosalpinx in recurrent miscarriage**
IRAS project ID:	**232650**
Protocol number:	**RG_17-150**
REC reference:	**17/WM/0444**
Sponsor	**University of Birmingham**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England and for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides details on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

IRAS project ID	232650

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from the HRA website.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found through IRAS.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to applicants and sponsors. You are invited to give your view of the service you have received and the application

IRAS project ID	232650

procedure. If you w sh to make your v ews known p ease use the feedback form ava ab e on the HRA webs te.

HRA Training

We are p eased to we come researchers and research management staff at our tra n ng days – see deta s on the HRA webs te.

Your IRAS project ID s **232650**. P ease quote th s on a correspondence.

Yours s ncere y

Miss Lauren Allen
Assessor

Ema : hra.approva @nhs.net

Copy to: *Dr Sean Jennings (Sponsor contact)*
Mrs Kelly Hard, Birmingham Women's Hospital (Lead NHS R&D contact)

IRAS project ID	232650

Appendix A - List of Documents

The f na document set assessed and approved by HRA Approva s sted be ow.

Document	*Version*	*Date*
Ev dence of Sponsor nsurance or ndemn ty (non NHS Sponsors on y) [Sponsor Insurance Conf rmat on Letter]	1.0	14 November 2017
GP/consu ant nformat on sheets or etters [GP INFORMATION SHEET V1.0 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age]	1.1	28 December 2017
GP/consu ant nformat on sheets or etters [GP INFORMATION SHEET V1.1 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age (w th changes accepted)]	1.1	28 December 2017
HRA Schedu e of Events [HRA Scedu e of events The ro e of hydrosa p nx n recurrent m scarr age IRAS ID 232650]	1.0	15 December 2017
HRA Statement of Act v t es	1.2	21 December 2017
IRAS App cat on Form [IRAS_Form_20112017]		20 November 2017
Letter from funder [fund ng etter 1]		
Letter from funder [fund ng etter 2]		
Letter from funder [grant etter]		
Letter from sponsor [Sponsor Conf rmat on Letter]	1.0	14 November 2017
Non va dated quest onna re [Pregnancy outcome data co ect on form]	1.1	28 December 2017
Non va dated quest onna re [PREGNANCY OUTCOME DATA COLLECTION FORM V1.1 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age (w th changes accepted)]	1.1	28 December 2017
Other [PROTOCOL V1.1 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age (w th changes accepted)]	1.1	28 December 2017
Other [Emp oyers L ab ty Insurance]	1.0	15 Ju y 2017
Other [Gener c Insurance Letter]	1.0	15 Ju y 2017
Other [Pub c & Products L ab ty Cert f cate]	1.0	15 Ju y 2017
Part c pant consent form [PATIENT CONSENT FORM v1.0 IRAS ID 232650 The ro e of hydrosa p nx n recurrent m scarr age]	1.1	28 December 2017
Part c pant consent form [PATIENT CONSENT FORM v1.1 IRAS ID 232650 The ro e of hydrosa p nx n recurrent m scarr age (w th accepted changes)]	1.1	28 December 2017
Part c pant nformat on sheet (PIS) [PATIENT INFORMATION SHEET V1.0 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age]	1.1	28 December 2017
Part c pant nformat on sheet (PIS) [PATIENT INFORMATION SHEET V1.1 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age (w th changes accepted)]	1.1	28 December 2017
Referee's report or other sc ent f c cr t que report [Interna Peer rev ew form J Ghosh by Prof TJ C ark]	1.0	18 Ju y 2017
Research protoco or project proposa [PROTOCOL V1.0 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age]	1.1	28 December 2017
Summary CV for Ch ef Invest gator (CI) [Prof A Coomarasamy 2 page CV]	1.0	17 September 2017
Summary CV for student [Dr J Ghosh 2 page summary CV Oct 2017]	1.0	27 October 2017
Summary CV for supervsor (student research) [Prof A Coomarasamy 2 page summary CV as CI and Supervsor]	1.0	01 October 2017

IRAS project ID	232650

Summary CV for supervisor (student research) [Dr I D Ga os 2 page CV August 2017]		17 September 2017
Summary CV for supervisor (student research) [Dr J J Chu CV 2 page summary Sept 2017]		17 September 2017

IRAS project ID	232650

Appendix B - Summary of HRA Assessment

Th s append x prov des assurance to you, the sponsor and the NHS n Eng and that the stu dy, as rev ewed for HRA Approva , s comp ant w th re evant standards. It a so prov des nformat on and c ar f cat on, where appropr ate, to part c pat ng NHS organ sat ons n Eng and to ass st n assess ng and arrang ng capac ty and capab ty.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The fo ow ng person s the sponsor contact for the purpose of address ng part c pat ng organ sat on quest ons re at ng to the study:

Name: Dr Sean Jenn ngs

Te

Ema : researchgovernance@contacts.bham.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards?	Comments
1.1	IRAS app cat on comp eted correct y	Yes	No comments
2.1	Part c pant nformat on/consent documents and consent process	Yes	No comments
3.1	Protoco assessment	Yes	No comments
4.1	A ocat on of respons b t es and r ghts are agreed and documented	Yes	The Statement of Act v t es and Schedu e of Events w act as the agreement between the sponsor and s te.
4.2	Insurance/ ndemn ty arrangements assessed	Yes	Where app cab e, ndependent contractors (e.g. Genera Pract t oners) shou d ensure that the profess ona ndemn ty prov ded by the r med ca defence organ sat on covers the act v t es expected of them for th s

IRAS project ID	232650

Section	HRA Assessment Criteria	Compliant with Standards?	Comments
			research study
4.3	F nanc a arrangements assessed	Yes	No fund ng w be prov ded to the s te.
5.1	Comp ance w th the Data Protect on Act and data secur ty ssues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for comp ance w th the C n ca Tr a s Regu at ons assessed	Not App cab e	No comments
5.3	Comp ance w th any app cab e aws or regu at ons	Yes	Vag na swabs w be transferred to a Research T ssue Bank at the end of the research. Part c pant dent f ers w be removed before the samp es are transferred.
6.1	NHS Research Eth cs Comm ttee favourab e op n on rece ved for app cab e stud es	Yes	No comments.
6.2	CTIMPS – C n ca Tr a s Author sat on (CTA) etter rece ved	Not App cab e	No comments
6.3	Dev ces – MHRA not ce of no object on rece ved	Not App cab e	No comments
6.4	Other regu atory approva s and author sat ons rece ved	Not App cab e	No comments

IRAS project ID	232650

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
There s one s te type. A study act v ty w be conducted at the s te as deta ed n the Protoco and support ng documents. The Ch ef Invest gator or sponsor shou d share re evant study documents w th part c pat ng NHS organ sat ons n Eng and n order to put arrangements n p ace to de ver the study. The documents shou d be sent to both the oca study team, where app cab e, and the off ce prov d ng the research management funct on at the part c pat ng organ sat on. For NIHR CRN Portfo o stud es, the Loca LCRN contact shou d a so be cop ed nto th s correspondence. For further gu dance on work ng w th part c pat ng NHS organ sat ons p ease see the HRA webs te. If ch ef nvest gators, sponsors or pr nc pa nvest gators are asked to comp ete s te eve forms for part c pat ng NHS organ sat ons n Eng and wh ch are not prov ded n IRAS or on the HRA webs te, the ch ef nvest gator, sponsor or pr nc pa nvest gator shou d not fy the HRA mmed ate y at hra.approva@nhs.net. The HRA w work w th these organ sat ons to ach eve a cons stent approach to nformat on prov s on.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.
Part c pat ng NHS organ sat ons n Eng and **will be expected to formally confirm their capacity and capability to host this research**. • Fo ow ng ssue of th s etter, part c pat ng NHS organ sat ons n Eng and may now conf rm to the sponsor the r capac ty and capab ty to host th s research, when ready to do so. How capac ty and capac ty w be conf rmed s deta ed n the *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sect on of th s append x. • The Assess ng, Arrang ng, and Conf rm ng document on the HRA webs te prov des further nformat on for the sponsor and NHS organ sat ons on assess ng, arrang ng and conf rm ng capac ty and capab ty.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Pr nc pa Invest gator (PI) shou d be dent f ed at the s te. The sponsor has conf rmed the PI w need to have NIHR CRN tra n ng n Good C n ca Pract ce, nc ud ng nformed consent tra n ng GCP tra n ng s not a gener c tra n ng expectat on, n ne w th the HRA/MHRA statement on tra n ng expectat ons.

IRAS project ID	232650

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
Access arrangements w not be app cab e as the study act v ty w be conducted by staff at the s te.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
• The app cant has nd cated that they ntend to app y for nc us on on the NIHR CRN Portfo o.

Appendix 9: Confirmation of capacity and capability from Birmingham Women's and Children's NHS Foundation Trust Research and Development office for "The role of hydrosalpinx in recurrent miscarriage"

Research and Development
Birmingham Women's and Children's NHS Foundation Trust
Birmingham Women's Hospital
Mindelsohn Way
Edgbaston Birmingham B15 2TG
Tel: 0121 472 1377
BWC.research@bch.nhs.uk

16th February 2018

Dr Jayasish Ghosh
Gynaecology and Obstetrics
Birmingham Women's and Children's NHS Foundation Trust

Dear Jay

Re: Birmingham Women's and Children's Hospital NHS Foundation Trust R&D Confirmation of Capacity and Capability

Project Title: The role of hydrosalpinx in recurrent miscarriage
IRAS Ref : 232650
REC Reference: 17/WM/0444
R&D No : 17/BW/GYN/PO48

Thank you for informing Birmingham Women's and Children's NHS Foundation Trust's R&D office of the above project

can confirm that Birmingham Women's and Children's NHS Foundation Trust has the capacity and capability to deliver the above referenced study and therefore is issuing R&D Confirmation of Capacity and Capability

Please find attached our agreed Statement of Activities as confirmation

R&D Confirmation of Capacity and Capability of the study is subject to the following conditions

- f you have not already done so you must ensure that you and other members of the research team complete Good Clinical Practice ('GCP') training and a copy of your certificate is forwarded to the R&D Department before conducting your research
- The research is conducted in line with the guidance given within the UK Policy Framework for Health and Social Care Research and where appropriate the Medicines for Human Use (Clinical Trial) Regulations 2004 You must also apply with the principles of CH Good Clinical Practice in conduct of your research
- The research will be conducted in compliance with Trust Policies and carried out in accordance with the Data Protection Act (1998) Human Tissue Act 20014 Health & Safety at Work Act and the Caldicott principles and NHS Code of Confidentiality
- Any proposed changes or amendments to the protocol will be notified to the ethics committee the research sponsor and the R&D Manager/R&D Facilitator
- The UK Policy Framework for Health and Social Care Research published by the Health Research Authority (HRA) and the UK Health Departments make clear that appropriate

a ocat on of respons b ty, and c ear understand ng of respons b ty s fundamenta to good overa governance of research. You must ensure that a researchers not emp oyed by the Trust fo ow the standard sed procedures for ssu ng Honorary Research Contracts (HRC) or Letters of Access (LOA) as a d down n the Research n the HR Good Pract ce Resource Pack http://www.n hr.ac.uk/po cy and standards/research passports.htm

- Procedures are n p ace to ensure co ect on of h gh qua ty, accurate data and the ntegr ty and cond t ona ty of data dur ng process ng and storage.

- Upon comp et on of the research you must comp ete an End of Study report and subm t th s to Eth cs and copy n the R&D Manager/R&D Fac tator at Birmingham Women's and Children's NHS Foundat on Trust. http://www.hra.nhs.uk/research commun ty/end of study and beyond/not fy ng the end of study/

- If your project has been adopted by the Nat ona Inst tute for Hea th Research (NIHR) portfo o you w be requ red to prov de month y recru tment f gures to the R&D Off ce and address any ssues affect ng recru tment.

- That the ch ef/Pr nc pa Invest gator and the research team shou d be fam ar w th BWC tr a Standard Operat ng Procedures. These SOPS can be found at the fo ow ng ocat on on the trust ntranet. http //eve/directorates/corporate/RD/Pages/Research-and-Development-SOPs-and-Policies aspx

- The study w be run as out ned n ro es and respons b t es sect on of the CI/PI Agreement wh ch has been du y s gned and returned to R & D

NIHR fund ng to prov ders of NHS serv ces s cond t ona on meet ng the 70 day benchmark to recru t f rst pat ent fo ow ng subm ss on of a comp ete oca package. The date for rece pt of a comp ete oca package for th s study was 09 February 2018. Th s therefore equates to a 70 day target date of 20 Apr 2018.

In order for the Trust to co ate the data on meet ng th s cond t on, p ease nform R&D when you recru t your f rst pat ent. P ease can you a so nform R&D of any c rcumstances outs de your contro that may affect your ab ty to ach eve th s target, such as sponsor de ays w th S te In t at on. The nformat on on both of the above aspects can be e ma ed to bwc.research@nhs.net

Documents approved:

Documents	Version	Date
Ev dence of Sponsor nsurance or ndemn ty (non NHS Sponsors on y) [Sponsor Insurance Conf rmat on Letter]	1.0	14 November 2017
GP/consu tant nformat on sheets or etters [GP INFORMATION SHEET V1.0 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age]	1.1	28 December 2017
GP/consu tant nformat on sheets or etters [GP INFORMATION SHEET V1.1 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age (w th changes accepted)]	1.1	28 December 2017
HRA Schedu e of Events [HRA Scedu e of events The ro e of hydrosa p nx n recurrent m scarr age IRAS ID 232650]	1.0	15 December 2017
HRA Statement of Act v t es	1.2	21 December 2017
IRAS App cat on Form [IRAS_Form_20112017]		20 November 2017
Letter from funder [fund ng etter 1]		

Letter from funder [fund ng etter 2]		
Letter from funder [grant etter]		
Letter from sponsor [Sponsor Conf rmat on Letter]	1.0	14 November 2017
Non va dated quest onna re [Pregnancy outcome data co ect on form]	1.1	28 December 2017
Non va dated quest onna re [PREGNANCY OUTCOME DATA COLLECTION FORM V1.1 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age (w th changes accepted)]	1.1	28 December 2017
Other [PROTOCOL V1.1 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age (w th changes accepted)]	1.1	28 December 2017
Other [Emp oyers L ab ty Insurance]	1.0	15 Ju y 2017
Other [Gener c Insurance Letter]	1.0	15 Ju y 2017
Other [Pub c & Products L ab ty Cert f cate]	1.0	15 Ju y 2017
Part c pant consent form [PATIENT CONSENT FORM v1.0 IRAS ID 232650 The ro e of hydrosa p nx n recurrent m scarr age]	1.1	28 December 2017
Part c pant consent form [PATIENT CONSENT FORM v1.1 IRAS ID 232650 The ro e of hydrosa p nx n recurrent m scarr age (w th accepted changes)]	1.1	28 December 2017
Part c pant nformat on sheet (PIS) [PATIENT INFORMATION SHEET V1.0 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age]	1.1	28 December 2017
Part c pant nformat on sheet (PIS) [PATIENT INFORMATION SHEET V1.1 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age (w th changes accepted)]	1.1	28 December 2017
Referee's report or other sc ent f c cr t que report [Interna Peer rev ew form J Ghosh by Prof TJ C ark]	1.0	18 Ju y 2017
Research protoco or project proposa [PROTOCOL V1.0 IRAS ID 232650 The ro e of hydrosa p nx n recurent m scarr age]	1.1	28 December 2017
Summary CV for Ch ef Invest gator (CI) [Prof A Coomarasamy 2 page CV]	1.0	17 September 2017
Summary CV for student [Dr J Ghosh 2 page summary CV Oct 2017]	1.0	27 October 2017
Summary CV for superv sor (student research) [Prof A Coomarasamy 2 page summary CV as CI and Superv sor]	1.0	01 October 2017
Summary CV for superv sor (student research) [Dr I D Ga os 2 page CV August 2017]		17 September 2017
Summary CV for superv sor (student research) [Dr J J Chu CV 2 page summary Sept 2017]		17 September 2017

May I a so draw your attent on to the UK Po cy Framework for Hea th and Soc a Care Research wh ch can be found on the nternet https://www.hra.nhs.uk/p ann ng and mprov ng research/po c es standards eg s at on/uk po cy framework hea th soc a care research/ and rem nd you that a research w th n the Trust shou d be run to the standards as out ned n th s document. Gu dance and

adv ce s a ways ava ab e from the Department of Research and Deve opment shou d you requ re t at any stage of your project.

Your research act v ty s now covered by NHS ndemn ty as set out n HSG (96) 48, and your tr a has been entered into the Trusts' database.

The Trust conducts regu ar aud ts to mon tor 10% of a projects on an annua bas s. You must comp y w th the requests as they have the author ty to aud t your s te f es at any t me.

If you have any quer es re at ng to R&D, p ease do not hes tate to contact me. The Trust w shes you success w th your research.

Yours s ncere y

Ke y Hard
Head of Research & Development

Cc. Sean Jenn ngs (sponsor representat ve) & Arr Coomarasamy (Ch ef Invest gator)

Appendix 10: Notification of request for amendment for "The role of hydrosalpinx in recurrent miscarriage"

NHS
Health Research Authority

West Midlands - Edgbaston Research Ethics Committee
he Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

04 December 2018

Dr J Ghosh
Academ c Un t, 3rd F oor, B rm ngham Women's Hosp ta
M nde sohn Way
Edgbaston, B rm ngham
B15 2TG

Dear Dr Ghosh

Study title:	**The role of hydrosalpinx in recurrent miscarriage**
REC reference:	**17/WM/0444**
Protocol number:	**RG_17-150**
Amendment number:	**1**
Amendment date:	**08 August 2018**
IRAS project ID:	**232650**

Thank you for subm tt ng the above amendment, wh ch was rece ved on 03 December 2018. I can conf rm that th s s a va d not ce of a substant a amendment and w be rev ewed by the Sub Comm ttee of the REC at ts next meet ng.

Documents received

The documents to be rev ewed are as fo ows:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CT MP) [RAS D 232650 ammendment form F NAL pdf]	1	08 August 2018
Participant consent form [PAT ENT CONSENT FORM v1 2 RAS D 232650 The role of hydrosalpinx in recurrent miscarriage doc]	1 2	08 August 2018
Participant consent form [PAT ENT CONSENT FORM v1 2 RAS D 232650 The role of hydrosalpinx in recurrent miscarriage - clean version with accepted changes doc]	1 2	08 August 2018
Participant information sheet (P S) [PAT ENT NFORMAT ON SHEET V1 2 RAS D 232650 The role of hydrosalpinx in recurent miscarriage - clean version with accepted changes docx]	1 2	08 August 2018
Participant information sheet (P S) [PAT ENT NFORMAT ON SHEET V1 2 RAS D 232650 The role of hydrosalpinx in recurent miscarriage docx]	1 2	08 August 2018
Research protocol or project proposal [PROTOCOL V1 2 RAS D 232650 The role of hydrosalpinx in recurent miscarriage - clean version with accepted changes docx]	1 2	08 August 2018
Research protocol or project proposal [PROTOCOL V1 2 RAS D 232650 The role of hydrosalpinx in recurent miscarriage docx]	1 2	08 August 2018

Notification of the Committee's decision

The Comm ttee w ssue an eth ca op n on on the amendment w th n a max mum of 35 days from the date of rece pt.

R&D approval

A nvest gators and research co aborators n the NHS shou d not fy the R&D off ce for the re evant NHS care organ sat on of th s amendment and check whether t affects R&D approva for the research.

We are p eased to we come researchers and R & D staff at our Research Eth cs Serv ce Committee members' training days – see deta s at http://www.hra.nhs.uk/hra tra n ng/

17/WM/0444:	**Please quote this number on all correspondence**

Yours s ncere y

Ellena Stansbury
REC Assistant

Ema : NRESComm ttee.WestM d ands Edgbaston@nhs.net

Copy to: *Mrs Kelly Hard, Birmingham Women's Hospital*

Appendix 11: IRAS amendment form for "The role of hydrosalpinx in recurrent miscarriage"

Notice of Amendment IRAS Version 5.9.1

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the ques ions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
The role of hydrosalpinx in recurrent miscarriage

1. Is your project research?

(•) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product
( ) Clinical investigation or other study of a medical device
( ) Combined trial of an investigational medicinal product and an investigational medical device
( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
(•) Basic science study involving procedures with human participants
( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
( ) Study involving qualitative methods only
( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
( ) Study limited to working with data (specific project only)
( ) Research tissue bank
( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (•) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(•) No
b) Will you be taking new human tissue samples (or other human biological samples)?	(•) Yes	( ) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(•) No

d) Will the study involve any other clinical procedures with participants (e.g. MRI, ultrasound, physical examination)? (●) Yes ( ) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- [x] England
- [ ] Scotland
- [ ] Wales
- [ ] Nor hern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (●) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve he NHS

4. Which applications do you require?

IMPORTANT: If your project is taking place in the NHS and is led from England select 'IRAS Form'. If your project is led from Northern Ireland, Scotland or Wales select 'NHS/HSC Research and Development Offices' and/or relevant Research Ethics Committee applications, as appropriate.

- [x] IRAS Form
- [ ] Confidentiality Advisory Group (CAG)
- [ ] Her Majesty's Prison and Probation Service (HMPPS)

For NHS/HSC R&D Offices in Northern Ireland, Scotland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in addition to the study wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisations in England different arrangements apply for the provision of site specific information. Refer to IRAS Help for more information.

Most research projects require review by a REC within the UK Health Departments' Research Ethics Service. Is your study exempt from REC review?

( ) Yes (●) No

5. Will any research sites in this study be NHS organisations?

(●) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or a Diagnostic Evidence Co-operative in all study sites?

Please see information button for further details.

( ) Yes (●) No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

(•) Yes ( ) No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

( ) Yes (•) No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

( ) Yes (•) No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

( ) Yes (•) No

9. Is the study or any part of it being undertaken as an educational project?

(•) Yes ( ) No

Please describe briefly the involvement of the student(s):
Dr Jayasish Ghosh (applicant) will be using this as part of his PhD which will be supervised by Prof A Coomarasamy

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

(•) Yes ( ) No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

( ) Yes (•) No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

Yes No

Notice of Amendment IRAS Version 5.9.1

NOTICE OF SUBSTANTIAL AMENDMENT

Please use this form to notify the main REC of substantial amendments to all research other than clinical trials of investigational medicinal products (CTIMPs).
The form should be completed by the Chief Investigator using language comprehensible to a lay person.

Details of Chief Investigator:

	Title Forename/Initials Surname
	Prof A Coomarasamy
Work Address	Academic Unit, 3rd Floor, Birmingham Women's Hospital
	Mindelsohn Way
	Edgbaston, Birmingham
PostCode	B15 2TG
Email	
Telephone	
Fax	

For guidance on this section of the form refer to the guidance

Full title of study:	The role of hydrosalpinx in recurrent miscarriage
Lead sponsor:	University of Birmingham
Name of REC:	West Midlands Edgbaston
REC reference number:	17/WM/0444

International Standard Randomised Controlled Trial Number (ISRCTN):	
ClinicalTrials.gov Identifier (NCT number):	

Additional reference number(s):

Ref.Number Description	Reference Number
University of Birmingham Research Governance Ref Number	RG_17-150
University of Birmingham Research Support Group Ref Number	ERN_17-1086

Name of lead R&D office:	Birmingham Women's Hospital
Date study commenced:	28/2/18
Protocol reference (if applicable), current version and date:	v1.1 28th Dec 2017

Amendment number and date: v1.2 8th Aug 2018

Type of amendment

(a) Amendment to information previously given in IRAS

◉ Yes ○ No

If yes, please refer to relevant sections of IRAS in the "summary of changes" below.

Please see summary of changes for details of proposed changes

(b) Amendment to the protocol

◉ Yes ○ No

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

Revised protocol with tracked changes v1.2 8th August 2018 enclosed

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

◉ Yes ○ No

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Revised PIS V1.2 8th August 2018 and Revised Consent form V1.2 8th August 2018 enclosed

Is this a modified version of an amendment previously notified and not approved?

○ Yes ◉ No

Summary of changes

Briefly summarise the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study.
If this is a modified amendment, please explain how the modifications address the concerns raised previously by the ethics committee.
If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

1) Changing the Primary Investigator to Dr Jayasish Ghosh from Prof Arri Coomarasamy for organisational purposes. This does not affect the study methodology or design.

2) A31 - Currently women are being sent the patient information leaflet in the post. However, we have found many women are not reading the patient information leaflet before their appointment as there is a significant amount of other information also in their appointment pack. Many women also want to consent on the day of their appointment to avoid having to come back at a later date to consent. The amendment proposes that they will also be given the patient informa ion leaflet to read on the day of he appointment to read whilst they wait to be seen and would be able to consent on the day. Involvement in the trial only requires consenting to have a Hysterosalpingo-contrast-sonogram (HyCoSy) and a follow up to discuss their ongoing fertility history. There is significant cross over between the recurrent miscarriage population and the fertility population. Many patients are seen and treated by both recurrent miscarriage and fertility teams and a HyCoSy is a routine fer ility investigation which would ordinarily not require formal written consent or a cooling off period and may be ordered in these patients. The patients would of course still have the option of being consented at a later date if they wanted to. This amendment would streamline the consent process for women who are happy to consent on the day of their clinic appointment. This does not affect the study design or methodology.

3) A6-2, A13, A22 and Part B: Section 5, Question 1. Currently women have their Hysterosalpingo-contrast-sonogram (HyCoSy) are having 2 swabs, a high vaginal swab taken by a doctor and a self-taken vulvo-vaginal swab. The amendment is that only a self-taken vulvo-vaginal swab is taken. There is no significant change to the study design or methodology. The purpose of the is to bring the process of performing the scan into line with NICE Clinical Guideline

number 156 recommendations that only a vulvo-vaginal swab for C. trachomatis is taken prior to uterine instrumentation. It is also more convenient and less intrusive for women as a formal vaginal speculum examination is not required.

4) Part B: Section 5, Question 9. The testing will also only be Nucleic Acid Amplification Testing (NAATs) which has the highest sensitivity for detection of pathogens as detailed in the new protocol v1.2 08/Aug/2018. There is no change to study design or methodology. The other microbiology tests are no longer required as only testing for C. trachomatis is required by NICE.

5) A6-2, A13 and A22. The HyCoSy scan will be performed immediately after menstruation and before unprotected intercourse has occurred in that menstrual cycle. This is because the technical quality of the scan is improved if performed when the endometrium is thin in the early proliferative phase of the menstrual cycle and is normal practice where they are performed for non-research purposes. This will also remove the risk of a pregnancy which has not yet implanted into the endometrium of the womb and so would not yet show up on a urine pregnancy test. Urine pregnancy tests will herefore no longer be required as here is no risk of pregnancy at the time of performing the scan. This does not change the study design or methodology.

6) A6-2, A13 and A22. Patients will have the HyCoSy in addition to their routine ultrasound pelvis. As HyCoSys are timed to a woman's menstrual cycle some women are forgetting to contact the research team to receive their HyCoSy before their next follow-up. Meaning they are coming to clinic for a follow up without their complete set of investigations. A normal ultrasound pelvis does not need to be timed to a menstrual cycle and so this amendment would mean no women would turn up for a follow up without their complete set of routine investigations.

7) Part B: Section 5, Question 13, 14. – The self-taken vulvo-vaginal swab will be disposed of after testing as per Birmingham Women's and Children's Hospital Pathology standard operating procedure.

Any other relevant information

Applicants may indicate any specific issues relating to the amendment, on which the opinion of a reviewing body is sought.

Nil

List of enclosed documents

Document	*Version*	*Date*
PROTOCOL V1.2 IRAS ID 232650 The role of hydrosalpinx in recurent miscarriage	v1.2	08/08/2018
PATIENT INFORMATION SHEET V1.2 IRAS ID 232650 The role of hydrosalpinx in recurent miscarriage	v1.2	08/08/2018
PATIENT CONSENT FORM v1.2 IRAS ID 232650 The role of hydrosalpinx in recurrent miscarriage	v1.2	08/08/2018

Declaration by Chief Investigator

1. *I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.*
2. *I consider that it would be reasonable for the proposed amendment to be implemented.*

This section was signed electronically by Dr Arri Coomarasamy on 09/11/2018 16:19.

Job Title/Post: Professor of of Gynaecology

Organisation: University of Birmingham

Email:

Declaration by the sponsor's representative

I confirm the sponsor's support for this substantial amendment.

This section was signed electronically by Mr David Law on 23/11/2018 15:20.

Job Title/Post:	Research Governance Officer
Organisation:	University of Birmingham
Email:	researchgovernance@contacts.bham.ac.uk

Appendix 12 Protocol v1.2. for "The role of hydrosalpinx in recurrent miscarriage"

The role of hydrosalpinx in recurrent miscarriage

PROTOCOL

Version 1.2

8th August 2018

Chief Investigator

Professor Arri Coomarasamy

Tel:

Email:

Key contacts:

- The CI is responsible for the medical oversight of the study.
- Professor Arri Coomarasamy is the Director of the Tommy's National Centre for Miscarriage Research
- Dr. Adam Devall is the Trial Manager for Tommy's National Centre for Miscarriage Research: 0797 182 3452; a.j.devall@bham.ac.uk
- Mr David Law is the Head of the Research Support Group for the University of Birmingham: 0121 414 2644; researchgovernance@contacts.bham.ac.uk

Table of Contents

The role of hydrosalpinx in recurrent miscarriage study design group 3
Principal Investigator & Chief Investigator 3
Study Design and Management 3
Co-Investigators 3
Background 4
Epidemiology of miscarriage 4
Tubal disease and its effect on reproductive outcomes 4
Detection of tubal disease 5
Rationale for this study 5
Objectives 6
Study Design 6
Population to be studied 6
Inclusion criteria 6
Exclusion criteria 6
Identifying Participants 6
Data to be collected and tests to be performed 6
Outcomes to be measured 7
Method of collection of data and outcomes 7
Consent to participation and feedback of results 8
Dissemination of study results 8
Withdrawal process 8
Patient Journey 8
Accrual and Analysis 9
Sample Size 9
Statistical Analysis 9
Data management and archiving 10
Safety reporting (Adverse Events and Serious Adverse Events) 10
Serious breaches 10
Insurance and indemnity 10
End of study definition 10
Study Oversight and Quality Assurance processes 11
Funding and Sponsorship 11
Study Flow Chart 12
List of References 13

Table of Contents

The role of hydrosalpinx in recurrent miscarriage study design group 3
Principal Investigator & Chief Investigator 3
Study Design and Management 3
Co-Investigators 3
Background 4
Epidemiology of miscarriage 4
Tubal disease and its effect on reproductive outcomes 4
Detection of tubal disease 5
Rationale for this study 5
Objectives 6
Study Design 6
Population to be studied 6
Inclusion criteria 6
Exclusion criteria 6
Identifying Participants 6
Data to be collected and tests to be performed 6
Outcomes to be measured 7
Method of collection of data and outcomes 7
Consent to participation and feedback of results 8
Dissemination of study results 8
Withdrawal process 8
Patient Journey 8
Accrual and Analysis 9
Sample Size 9
Statistical Analysis 9
Data management and archiving 10
Safety reporting (Adverse Events and Serious Adverse Events) 10
Serious breaches 10
Insurance and indemnity 10
End of study definition 10
Study Oversight and Quality Assurance processes 11
Funding and Sponsorship 11
Study Flow Chart 12
List of References 13

The role of hydrosalpinx in recurrent miscarriage study design group

Chief Investigator

Professor Arri Coomarasamy
Professor of Gynaecology, University of Birmingham
Birmingham Women's Hospital

Principal Investigator, Study Design and Management

Dr Jayasish Ghosh
Clinical Research Fellow and Registrar in Obstetrics and Gynaecology
Birmingham Women's Hospital

Co-Investigators

Dr Ioannis D Gallos
Clinician Scientist in Reproductive Medicine and Honorary Consultant Gynaecologist and Sub-specialist in in Reproductive Medicine and Surgery
Birmingham Women's Hospital

Dr Justin J Chu
Academic Clinical Lecturer and Registrar in Obstetrics and Gynaecology
Birmingham Women's Hospital

Background

Epidemiology of miscarriage

Miscarriage, also known as spontaneous pregnancy loss before the fetus reaches viability, is a common early pregnancy complication. One in five pregnancies miscarries, which equates to over 250,000 miscarriages a year and 38,349 hospital admissions in the UK between April 1st 2015 and March 31st 2016.[1, 7] Miscarriage can be devastating to women and couples trying to conceive. It is a significant source of physical and psychological morbidity for many women and couples, the effects of which can endure for many months.[8] Yet for all the physical and mental sequelae and the economic costs, we have made little progress in treating this distressing condition.

Most miscarriages happen in the first 12 weeks of pregnancy because of sporadic chromosomal abnormalities.[9] However, for women with recurrent miscarriages, there may be genetic factors such as parental chromosomal abnormalities, embryonic chromosomal abnormalities, as well as structural anatomical abnormalities such as congenital uterine malformations causing miscarriage.[10-17] Other risk factors include endocrine disease such as diabetes, systemic and genital infections and thrombophilia such as Anti-Phospholipid Syndrome.[18, 19] The full list is recorded in appendix A for reference. However, despite very thorough investigation (full list of recommended investigations is outlined in Appendix B), a significant proportion of women with recurrent miscarriage will be labelled as unexplained and be left with no definitive answers, treatments or sometimes sadly, hope.[20]

Tubal disease and its effect on reproductive outcomes

C. trachomatis is the most common sexually transmitted infection in the UK.[2] *C. trachomatis* often has no symptoms, but can have serious health consequences, including fallopian tube damage. Untreated *C. trachomatis* infection in pregnancy may increase the risk of miscarriage, preterm birth, low birth weight and stillbirth.[4-6]

A severe form of tubal damage is when the tube is blocked and filled with fluid, a condition called hydrosalpinx. They are classically caused by ascending infections from the lower genital tract such as chlamydia, which cause pelvic inflammatory disease, causing the tubes to appear swollen and enlarged.[21] Hydrosalpinx is associated with a dramatic reduction in the chances of a live birth with assisted reproductive techniques.[22] This is explained by reduced implantation chances and increased pregnancy losses in the presence of a hydrosalpinx.[22] It is therefore strongly recommended that hydrosalpinges are removed or treated by tubal surgery prior to IVF.[23]

It has been suggested that hydrosalpinx may have a causative role in recurrent miscarriage. The biological rationale for this increase in pregnancy losses is not yet well understood. It has been postulated that the hydrosalpinx fluid may be embryotoxic as it can include micro-organisms, endotoxins, cytokines and free radicals causing oxidative stress.[24, 25] This fluid may therefore alter the endometrial receptivity causing a disturbed cytokine cascade, which impedes implantation.[26] Additionally, as the fallopian tube is occluded distally, the hydrosalpinx fluid may drain into the endometrial cavity having a flushing effect on the developing embryo hindering implantation.[27]

Detection of tubal disease

Investigation of suspected tubal disease is currently recommended for women with subfertility by laparoscopy or hysterosalpingography (HSG).[23] Women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered HSG to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion, and it is less invasive and makes more efficient use of resources than laparoscopy.[23] A HSG involves the passage of a radio-opaque contrast media through the female cervix whilst simultaneously taking serial radiographs to examine the patency and free spill of the media into the abdominal cavity. It requires radiographers, specialist radiographic equipment and exposure to radiation. Furthermore, a HSG is performed in a radiology department and requires a radiologist to interpret them.

Where appropriate expertise is available, screening for tubal occlusion using hysterosalpingo-contrast-ultrasonography (HyCoSy) can be considered because it is an effective alternative to HSG for women who are not known to have comorbidities.[23] A HyCoSy is an outpatient procedure which only requires a special contrast media and an USS machine which is usually present in most gynaecological out-patient departments. It is performed at the same time as a pelvic ultrasound, which is recommended for both women with subfertility or recurrent miscarriages.[20, 23] The contrast media is injected through the cervix and its flow into the uterus and out through the fallopian tubes is tracked in real time using the ultrasound machine to detect tubal patency and pathology. A HyCoSy is a standard investigation for fertility problems.

Laparoscopy is an invasive operative investigation where by a fibre optic camera inserted through the umbilicus is used to directly visualise the passage of dye through the fallopian tubes thereby confirming their patency and function. Women who are thought to have comorbidities should be offered laparoscopy and dye so that tubal and other pelvic pathology can be assessed and treated at the same time. Laparoscopy costs the NHS significantly more than HSG or HyCoSy and carries more risk. Costs associated with laparoscopy are in the form of theatre use and staffing, equipment used, recovery facilities and a ward bed.

In addition to the tubal investigations mentioned above, it is also necessary to identify whether women undergoing these investigations have concurrent genital tract infection before undertaking tubal assessment. Tests to diagnose genital *C. trachomatis* infections have evolved rapidly and nucleic acid amplification tests (NAAT), such as polymerase chain reaction (PCR) are now widely available. NAAT has been estimated to have a sensitivity of over 90% and a specificity of 99%, regardless of sampling from a cervical swab or by urine specimen.[28] A screen for *C. trachomatis* infection is recommended before women undergo any form of uterine instrumentation.[23]

Rationale for this study

Miscarriage affects one in five pregnancies and little progress has been made in understanding and treating this distressing condition.[1] *C. trachomatis* is the most common sexually transmitted infection in the UK.[2] *C. trachomatis* infection can have serious health consequences, including fallopian tube damage. Untreated *C. trachomatis* infection and tubal damage have been associated with miscarriage and adverse pregnancy outcomes such as preterm birth, low birth weight and stillbirth.[4-6] A cohort study is needed to establish the prevalence of tubal disease in women with recurrent miscarriages. HyCoSy will be performed to identify tubal disease and establish the magnitude of the problem in the

recurrent miscarriage population. The prognosis of tubal disease on miscarriage and other obstetric outcomes, and the role of medical interventions such as tubal surgery (to treat hydrosalpinx) on reducing miscarriage and adverse obstetric outcomes will also be studied.

Objectives

1. Establish the prevalence of hydrosalpinx in the recurrent miscarriage population.
2. Establish the prognosis of women diagnosed with recurrent miscarriage with concurrent hydrosalpinx.
3. Explore the role of tubal surgery for improving reproductive outcomes in women with recurrent miscarriage population and hydrosalpinx.

Study Design

This is a prospective observational cohort study.

Population to be studied

Potential participants will be approached at the Tommy's recurrent miscarriage clinic held at the Birmingham Women's Hospital.

Inclusion criteria

- Age 18-45
- Women diagnosed with recurrent miscarriage i.e. 2 or more miscarriages
- Ability to give informed consent

Such a wide inclusion criteria will enable a true assessment of the prevalence of hydrosalpinges in the recurrent miscarriage population.

Exclusion criteria

- Allergy to contrast media used for Hysterosalpingo-contrast-sonogram
- Allergy to sonographic gel used for ultrasound scanning
- Anatomical anomaly meaning transvaginal ultrasound scan not possible
- Stenosed/occluded cervix meaning contrast media unable to be introduced via cervix
- Inability to give informed consent
- Pregnant at the time of recruitment
- Declined recruitment

Identifying Participants

Patients will have been given the patient information leaflet prior to their appointment, when they are sent their appointment details letter or on the day of their appointment.

All women presenting to the clinic will be screened for the eligibility criteria by the routine healthcare provider. They will then be approached by Dr Jayasish Ghosh or one of the members of the research team and offered recruitment into the study.

Data to be collected and tests to be performed

- Screening for *Chlamydia trachomatis* – This is required as per NICE guidance prior to any uterine instrumentation to reduce the risk of subsequent pelvic inflammatory disease during

Hysterosalpingo-contrast-sonography.[23] The self-taken vulvo-vaginal swab which is the recommended specimen of choice by the British Association of Sexual Health and HIV (BASHH) for detection of *C. trachomatis* will then be sent to the microbiology laboratory of the Birmingham Women's Pathology department and will undergo testing for *C. Trachomatis and N. Gonorrhoea*.[29] These tests will be in the form of Nucleic Acid Amplification testing (NAATs) which has the highest levels of sensitivity compared to other forms of testing.[29] The storage and testing these swabs will be managed in line the Human Tissue Act, 2004.

- To establish the first objective of prevalence, recruited patients will be screened with a Hysterosalpingo-contrast-sonogram (HyCoSy) for the presence or absence of hydrosalpinges.

Outcomes to be measured

- To establish the second objective of prognosis of women with recurrent miscarriage and concurrent hydrosalpinges, pregnancy outcome data will be collected from both groups of patients (patients who screen positive and those who screen negative for hydrosalpinges). Specifically this will include:
    1. Biochemical pregnancy – a positive pregnancy test either on urine or serum pregnancy testing before ultrasound evidence of a gestational sac
    2. Clinical pregnancy – a pregnancy confirmed by evidence of a fetal heartbeat on ultrasound scan or using ultrasound parameters (ultrasound visualization of a gestational sac, embryonic pole with heartbeat).
    3. Pregnancy loss and at what gestation the pregnancy was lost – if unfortunately the patient suffered from a further miscarriage or still birth, the gestation in weeks of the loss will be noted
    4. Ectopic pregnancy – if a clinical pregnancy is seen on ultrasound scan but its location of implantation has taken place outside the uterine cavity, this is known as an ectopic pregnancy. Ectopic pregnancies are usually inside the fallopian tube although rarely they can be abdominal, ovarian or cervical.
    5. Live births – if fortunately a patient has a live birth this will be noted.
- To explore the role of tubal surgery, the same pregnancy outcomes listed above will be collected for the group of patients that were treated by their usual healthcare provider with surgery for their hydrosalpinges.

Method of collection of data and outcomes

- The screening for *Chlamydia trachomatis* will be performed by obtaining a self-taken vulvovaginal swab after informed consent has been gained.
- The presence or absence of hydrosalpinges will be noted at HyCoSy which will be performed after recruitment and informed consent has been gained. The scan will be performed immediately after the woman has menstruated and before she has had unprotected intercourse in that menstrual cycle. This is to avoid the risk of pregnancy or a fertilised embryo which has not implanted into the uterus yet, being flushed into the fallopian tubes. The HyCoSy will be performed by Dr Jayasish Ghosh, a General Medical Council and Royal College of Obstetricians and Gynaecologists registered registrar who is fully competent in such a procedure.

- The pregnancy outcome data listed above will be collected via a telephone consultation or email correspondence, conducted at 6 months and 12 months either post HyCoSy or post treatment. Should the patient not recall all of the information needed, she will be consented to examine her hospital patient records. Should the patient have had treatment at a different hospital trust, she would also have been consented to collect the specific information needed directly from that particular hospital's patient records.

Consent to participation and feedback of results

- The conduct of this study will be in accordance with the principles of Good Clinical Practice. All potential participants will be offered a patient information leaflet as well as a copy of the consent form. Participants will be made aware that they can withdraw from the trial at any stage and have their information destroyed.
- Patients will be informed of the results of their screening for *Chlamydia trachomatis* and appropriate treatment will be provided as necessary as per Birmingham Women's Hospital antimicrobial prescribing guidelines.
- HyCoSy findings will also be shared with the participants at the time of the scan. Any HyCoSy findings that may require urgent gynaecological attention will be referred to the on call gynaecology team at the Birmingham Women's Hospital with the patient's consent. Any other ultrasound findings that require non urgent follow up, will be shared with the GP or routine healthcare provider, with the patient's consent.

Dissemination of study results

The results of the study in terms of the prevalence of hydrosalpinges in the recurrent miscarriage population and the prognosis of women with recurrent miscarriage and concurrent hydrosalpinx will be disseminated to all participants via an email newsletter at the conclusion of the study. The results of comparing outcomes between patients who were treated for their hydrosalpinges versus those who were not, will be also be disseminated to all study participants and those who were not treated will be offered discussion about treatment after the conclusion of the study if treatment shows significant benefit.

Withdrawal process

Participants will be informed that they are able to withdraw from the study at any point without giving a reason and without any impact on their care, however, information gathered up until that point may be still used in the study.

Patient Journey

The patient will be sent the patient information leaflet at the same time as they receive the appointment letter thus ensuring sufficient time to read the written information related to the study before consent is taken. The patient will also be given the information leaflet when they come for their appointment and are waiting to be seen. They will have the option of consenting for recruitment on the day of their appointment or at a later date after a discussion with the research team. Written informed consent will be taken by good clinical practice trained research midwives, Dr Jayasish Ghosh, a General Medical Council and Royal College of Obstetricians and Gynaecologists registered registrar who is fully competent at taking consent and is also good clinical practice trained or other members of the research team who are registered with the General Medical Council and Royal College of

Obstetricians and Gynaecologists and are fully competent at taking consent and are also good clinical practice trained.

If a patient consents to participation, they will take a vulvo-vaginal swab in privacy, after appropriate instructions are given. If the swabs show an infection this will be treated as per the Birmingham Women's Hospital microbiology prescribing guidelines. At a subsequent appointment they will have a HyCoSy to detect the hydrosalpinges. A HyCoSy, as detailed in the background section above, incorporates a transvaginal ultrasound scan but is more detailed due to the use of contrast media to detect tubal and uterine pathology which may not be visible on normal transvaginal ultrasound. The result of which will be fed back to the patient and their usual clinician. They will then discuss with this clinician any treatment that maybe required.

If a hydrosalpinx is detected they will discuss with their usual clinician whether tubal surgery and what type would be appropriate. Surgery would then be carried out in the usual manner by the usual clinician. All patients would now be in one of three groups, those with no hydrosalpinx, those with a hydrosalpinx who did not have surgical treatment and those with a hydrosalpinx who did have surgical treatment of their hydrosalpinx. All three cohorts will then be followed up for 12 months as detailed in the method of collection of data and outcome section above. A pictorial representation of the patient journey is shown below in the study flow chart section.

Accrual and Analysis

Sample Size

We will attempt to recruit approximately 203 patients. For a prevalence survey in a condition where the prevalence is unknown, but it is not expected to be higher than 25% for obtaining a 95% level of confidence and precision at 0.05 we have estimated that 184 patients are required. To account for up to a 10% level of attrition, 203 patients should be recruited.

Statistical Analysis

For the prevalence survey of hydrosalpinx in the recurrent miscarriage population data will be presented using descriptive statistics. We will examine the prevalence data within subgroups created from clinical characteristics for example age, body mass index, previous sexually transmitted infections to identify high risk groups for hydrosalpinx.

For the comparison of the cohorts we will report numbers of individuals at each stage of study e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. The reasons for non-participation at each stage will be described. We will also describe the characteristics of study participants (e.g. demographic, clinical) and potential confounders (e.g. age, body mass index.) We will indicate the number of participants with missing data for each variable of interest and compute data for missing covariates using maximum likelihood estimation. We will summarise follow-up time (e.g. average and total amount) and report numbers of outcome events over time for each cohort. We will report unadjusted relative risk estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. at the 95% confidence interval). We will endeavour to translate estimates of relative risk into absolute risk for a meaningful time period. Subgroup analyses will be also performed according to the risk stratification described above.

Data management and archiving

The swab results and ultrasound records will be kept in locked surroundings at all times at the Birmingham Women's Hospital NHS Foundation Trust. A separate log will be kept which connects the patient identifiable data with the study allocation number and this will be destroyed at the end of the study period. Information will be collected on secured computers and all research team members will have had prior training in Good Clinical Practice.

All data originating from this research will be kept in secured, locked surroundings in the Academic Department of Birmingham Women's Hospital. Electronic data will be held on the University of Birmingham Network and it will be accessed through University of Birmingham computers. All results, records and data will be managed in line with the Data Protection Act, 1998 and the Human Tissue Act, 2004.

Safety reporting (Adverse Events and Serious Adverse Events)

Adverse events (AE) are defined as any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease. Occurrence of AEs will be recorded and reported to chief investigator. Any SAE will also be recorded in the study notes.

When an AE has occurred which is suspected to be a potential SAE, the Chief Investigator will assess the causality and severity of the AE. If the AE is confirmed as being a SAE, the CI will follow the University of Birmingham Standard Operating Procedures for SAE reporting, including reporting to the Sponsor. Follow-up of the event will continue until the event is considered resolved by all parties involved or a final outcome has been reached.

Serious breaches

In the unlikely event that a Serious Breach occurs, standard University of Birmingham procedures and SOPs for Serious Breach reporting will be followed.

Insurance and indemnity

The University of Birmingham purchases Clinical Trials Cover, which provides automatic cover for all Clinical Trials including those where the University accepts responsibility as sponsor, for any harm that comes about due to the University's, or its staff's negligence in relation to the design or management of the trial. In some cases, cover can also be provided in the case of non-negligent harm to participants.

End of study definition

Within 90 days of the final endpoint assessment of the final participant the main REC will be notified of the study's end and a summary of the clinical study report will be provided within 12 months of the end of the study. The study is expected to last three years.

Study Oversight and Quality Assurance processes

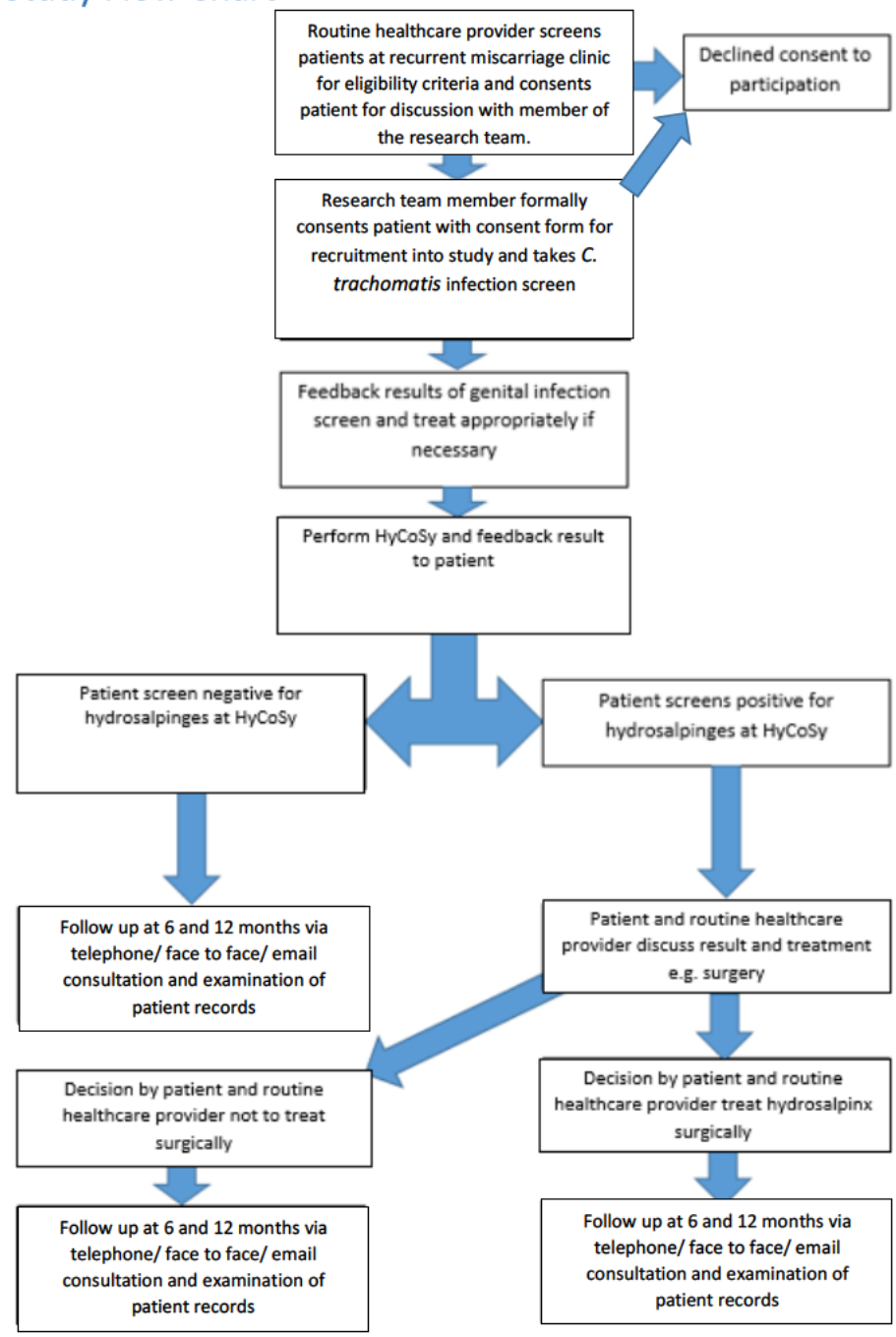
The Chief Investigator will oversee the quality of the study, and the study team will allow representatives of the Sponsor to monitor the study, including access to source documents as requested.

Funding and Sponsorship

Study funding is provided by Tommy's a UK charity that funds research into miscarriage, stillbirth and premature birth. *Tommy's National Centre for Miscarriage Research* is directed from The University of Birmingham by Professor Arri Coomarasamy but jointly hosted by three other UK universities, namely Imperial College London and The University of Warwick and is based at four NHS hospitals in Birmingham, Coventry and London. The partner institutions work closely with the University of Birmingham to ensure synergy and added value, whilst a vibrant programme of joint research meetings enables junior and senior colleagues to share disciplinary expertise and research news. The centre is seeking to understand why miscarriage happens, if it is likely to happen again, how to prevent it, and how to provide appropriate aftercare.

The University of Birmingham will be sponsoring this study (sponsorship reference number RG_ 17-150). *The University of Birmingham* is characterised by a tradition of innovation. Research at the University has broken new ground, pushed forward the boundaries of knowledge and made an impact on people's lives. The University was ranked 15th in the UK and 82nd in the world in the QS World University Rankings for 2016-17.

Study Flow Chart



List of References

1. Miscarriage Association. *Background information, Miscarriage.* Available from: https://www.miscarriageassociation.org.uk/media-queries/background-information/ [Accessed July 13th 2017]
2. Public Health England. *Sexually Transmitted Infections and Chlamydia Screening in England, 2016.* 2017. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/617020/Health_Protection_Report_STIs_NCSP_2017.pdf [Accessed: July 13th 2017]
3. Mamoun Kassabji, Jerry A. Sims, Lisa Butler, Suheil J. Muasher Reduced pregnancy outcome in patients with unilateral or bilateral hydrosalpinx after in vitro fertilization. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 1994; 56(2): 129-132. Available from: http://www.sciencedirect.com/science/article/pii/0028224394902690 [Accessed July 13th 2017]
4. Giakoumelou S, Wheelhouse N, Cuschieri K, Entrican G, Howie SE, Horne AW. The role of infection in miscarriage. *Hum Reprod Update*. 2016; 22(1): 116-33. doi:10.1093/humupd/dmv041.
5. Gravett MG, Nelson HP, DeRouen T, Critchlow C, Eschenbach DA, Holmes KK. Independent Associations of Bacterial Vaginosis and Chlamydia trachomatis Infection With Adverse Pregnancy Outcome. *JAMA.*1986; 256(14):1899-1903. doi:10.1001/jama.1986.03380140069024
6. Martin DH, Koutsky L, Eschenbach DA, Daling JR, Alexander ER, Benedetti JK, Holmes KK. Prematurity and Perinatal Mortality in Pregnancies Complicated by Maternal Chlamydia trachomatis Infections. *JAMA.*1982; 247(11):1585-1588. doi:10.1001/jama.1982.03320360035027
7. NHS Digital. *Hospital Maternity Activity 2015-2016.* 2016. Available from: http://content.digital.nhs.uk/searchcatalogue?productid=23494&q=%22nhs+maternity+statistics%22&topics=0%2fHospital+care&sort=Relevance&size=10&page=1#top [Accessed July 13th 2017]
8. Ingrid H. Lok, Richard Neugebauer, Psychological morbidity following miscarriage. *Best Practice & Research Clinical Obstetrics & Gynaecology.* 2007; 21(2): 229-247. doi:10.1016/j.bpobgyn.2006.11.007
9. M. Goddijn, N.J. Leschot. Genetic aspects of miscarriage. *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2000; 14(5): 855-865. Available from: http://dx.doi.org/10.1053/beog.2000.0124. [Accessed July 13th 2017]
10. de Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. *Hum Reprod.* 1990; 5(5): 519–28.
11. Clifford K, Rai R, Watson H, Regan L. An informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases. *Hum Reprod*. 1994; 9(7) :1328–32.
12. Mary D. Stephenson, Sony Sierra. Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. *Hum Reprod.* 2006; 21(4): 1076-1082. doi: 10.1093/humrep/dei417

13. Franssen MTM, Korevaar JC, van der Veen F, Leschot NJ, Bossuyt PMM, Goddijn M. Reproductive outcome after chromosome analysis in couples with two or more miscarriages: case-control study. *British Medical Journal*. 2006; 332(7544): 759-763. doi:10.1136/bmj.38735.459144.2F.

14. Carp, Howard et al. Karyotype of the abortus in recurrent miscarriage. *Fertility and Sterility*. 2001; 75(4): 678 – 682. Available from: http://dx.doi.org/10.1016/S0015-0282(00)01801-X [Accessed July 13th 2017]

15. M.D. Stephenson, K.A. Awartani, W.P. Robinson. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case–control study. *Hum Reprod*. 2002; 17(2): 446-451. doi: 10.1093/humrep/17.2.446

16. Grigoris F. Grimbizis, Michel Camus, Basil C. Tarlatzis, John N. Bontis, Paul Devroey. Clinical implications of uterine malformations and hysteroscopic treatment results. *Hum Reprod Update.* 2001; 7(2): 161-174. doi: 10.1093/humupd/7.2.161

17. R. Salim, L. Regan, B. Woelfer, M. Backos, D. Jurkovic. A comparative study of the morphology of congenital uterine anomalies in women with and without a history of recurrent first trimester miscarriage. *Hum Reprod.* 2003; 18(1): 162-166. doi: 10.1093/humrep/deg030

18. U Hanson et al. Relationship between Haemoglobin A1C in early type 1 (insulin-dependent) diabetic pregnancy and the occurrence of spontaneous abortion and fetal malformation in Sweden. *Diabetologia.* 1990; 33(2): 100-104.

19. R.S Rai, K. Clifford, H. Cohen, L. Regan; High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. *Hum Reprod.* 1995; 10(12): 3301-3304. doi: 10.1093/oxfordjournals.humrep.a135907

20. Regan L, Backos M, Rai R. *The Investigation and Treatment of Couples with Recurrent First trimester and Second-trimester Miscarriage*. Royal College of Obstetricians and Gynaecologists. Green-top Guideline No. 17. April 2011. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_17.pdf [Accessed July 13th 2017]

21. Willard Cates, Judith N. Wasserheit. Genital chlamydial infections: Epidemiology and reproductive sequelae. *American Journal of Obstetrics and Gynecology*. 1991; 164(6): 1771-1781. Available from: http://www.sciencedirect.com/science/article/pii/000293789190559A?showall%3Dtrue%26via%3Dihub [Accessed July 13th 2017]

22. Hulusi B Zeyneloglu, Aydin Arici, David L Olive. Adverse effects of hydrosalpinx on pregnancy rates after in vitro fertilization–embryo transfer. *Fertility and Sterility.* 1998; 70(3): 492-499.

23. National Institute for Health and Care Excellence. *Fertility problems: assessment and treatment for people with fertility problems.* NICE Clinical guideline No. 156. February 2013. Available from: https://www.nice.org.uk/guidance/cg156/evidence/full-guideline-pdf-188539453 [Accessed July 13th 2017]

24. A Strandell, A Sjögren, U Bentin-Ley, J Thorburn, L Hamberger, M Brännström. Hydrosalpinx fluid does not adversely affect the normal development of human embryos and implantation in vitro. *Hum Reprod.* 1998; 13(10): 2921-2925. doi: 10.1093/humrep/13.10.2921

25. Mohamed A. Bedaiwy, Jeffrey M. Goldberg, Tommaso Falcone, Mamta Singh, David Nelson, Hamdy Azab, Xia Wang, Rakesh Sharma. Relationship between oxidative stress and

embryotoxicity of hydrosalpingeal fluid. *Hum Reprod* 2002; 17(3): 601-604. doi: 10.1093/humrep/17.3.60

26. Sung, L., Copperman, A.B., Goldstein, M., Lapinski, R., Bustillo, M. and Mukherjee, T. Characterization of cytokines (IL-1α, IL-1β, IL-8, and TNF-α) in human hydrosalpinx fluid: a potential mechanism for embryo toxicity (abstract). *Fertil. Steril.* 1997; 1001(1997): S78
27. Mansour RT, Aboulghar MA, Serour GI, Riad R. Fluid accumulation of the uterine cavity before embryo transfer: a possible hindrance for implantation. *Journal of Assisted Reproduction and Genetics*. 1991; 8(3): 157-159.
28. J. R. Papp, J. Schachter, C. A. Gaydos, B. Van Der Pol. *Recommendations for the Laboratory-Based Detection of Chlamydia trachomatis and Neisseria gonorrhoeae*. Centres for Disease Control and Prevention. 63(RR02). March 2014. Available from https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6302a1.htm [Accessed July 13th 2017]
29. Nwokolo, N. Dragovic, B. Patel, S. Tong, CYW. Barker, G. Radcliffe, K. 2015 UK national guideline for the management of infection with Chlamydia trachomatis. *International Journal of STD & AIDS,* 2016, Vol. 27(4) 251–267. DOI: 10.1177/0956462415615443

Appendix 13: Patient information sheet v1.3 for "The role of hydrosalpinx in recurrent miscarriage"

PATIENT INFORMATION SHEET

The role of hydrosalpinx in recurrent miscarriage

Thank you for reading this leaflet.

We would like to invite you to take part in a study to investigate whether hydrosalpinx is associated with recurrent miscarriage. A hydrosalpinx is an abnormal swelling of a damaged fallopian tube. The fallopian tube carries the egg from the ovary (where it is stored and released), towards the uterus where it will meet the sperm. Hydrosalpinges can be caused by infections such as Chlamydia, infection of the pelvis, previous abdominal surgery and endometriosis.

Before you decide whether to take part we would like you to understand why the research is being done and what it will involve. Please take time to read this information leaflet. One of our team will go through the information sheet with you and answer any questions you may have.

What is the purpose of the study?

The aim of the study is to improve our understanding of why women maybe suffering from recurrent miscarriage and what we can do to help them.
We aim to find out;

1. How common hydrosalpinx is amongst women with recurrent miscarriage.
2. If women with hydrosalpinx are more likely to miscarry
3. If women with hydrosalpinx and recurrent miscarriage benefit from surgical treatment.

The information from this study may benefit all women who have suffered from miscarriage.

Why have I been invited?

Understanding why some women suffer from more than 1 miscarriage will help us to better treat this distressing condition. You have been invited to take part as you have been referred to our clinic because you have unfortunately suffered from recurrent miscarriage.

Do I have to take part and can I change my mind?

It is completely up to you to decide if you want to take part in the study or not. If you agree to take part we will request that you sign a written consent form. However, if you change your mind you can withdraw from the study at any time, without having to give a reason. Your decision will be documented and signed by a member of staff. Your choice will not affect the standard of your medical care in any way.

What will happen if I choose to take part?

After signing the consent form and with your agreement we will inform your GP that you have chosen to participate in this study. You will be given a dedicated telephone number to contact the research team on. We will ask you to take a self-taken vulvo-vaginal swabs to check for infections and treat the infection if any is found.

The Steps involved in taking this swab are as follows.

Step 1. Open kit and remove tube and package with orange writing. Remove the swab from the package. Do not touch the tip of the swab.

Step 2. Put the tip of the small swab about 2 inches into the opening of your vagina and make two small, slow circles with the tip. Make sure the swab touches the sides of your vagina. Take the swab out of your vagina.

Step 3. Remove cap from test tube. Place swab in test tube. Make sure the tip of the swab reaches the bottom of the tube. Do not puncture the foil cap. Break swab shaft at the score mark

Step 4. Put cap back tightly on test tube to prevent any leaking. Try not to splash the liquid out the tube.

Step 5. Discard wrappers. Wash your hands. Return the tube to the health worker.

At the next appointment we will perform a specialised internal ultrasound scan to look at your pelvic anatomy called a Hysterosalpingo-contrast Sonogram or HyCoSy for short. The HyCoSy scan needs to be performed straight after your period finishes and before you have unprotected vaginal sexual intercourse in that menstrual cycle to avoid the risk of pregnancy. If we find any abnormalities that are outside of the scope of this study, with your consent, we will pass the information onto the relevant healthcare team.

If a hydrosalpinx (a swollen damaged fallopian tube) is not found, with your consent, we will arrange a telephone/ face to face/ email consultation in 6 months and 12 months to see if you have managed to fall pregnant and what the outcome of the pregnancy was.

If a hydrosalpinx was found, we will inform you and your normal doctor who is looking after you in the recurrent miscarriage clinic. They will discuss and decide in conjunction with yourself, whether to treat the hydrosalpinx which may include surgery. We will then arrange, with your consent, a telephone/ face to face/ email consultation in 6 and 12 months to see if you have managed to fall pregnant and what the outcome of the pregnancy was, whether you have had treatment or not.

If you have a hydrosalpinx but opted not to have treatment, at the end of the study if we find out that treatment of hydrosalpinges does have benefits in terms of reducing the risk of further miscarriage, you will be given the option of re-discussing treatment with the doctor looking after you in the recurrent miscarriage clinic. Please be assured that information collected in the study will remain strictly confidential, adhering to all applicable University of Birmingham and Birmingham Women's Hospital policies and procedures.

What will happen to the self-taken vulvo-vaginal swab and how will the results of the swab and scan be stored?

Each swab will be labelled with your individual details and transported in an appropriate container to a laboratory for immediate analysis or storage as per the Birmingham Women's Hospital Pathology Laboratory standard operating procedure and in compliance with the Human Tissue Act 2004. The swab will be analysed for infection at the Birmingham Women's Hospital. The results of the swabs and scan will be stored indefinitely on secure information systems at The Birmingham Women's Hospital, as would any normal swabs or scans that occur during your treatment.

Who can look at my information?

Your consent form will be filed in the study site file. The results of the tests will be viewed by the Tommy's research team, who are outside of the direct care team, as well as the direct care team and all clinical information will be kept strictly confidential. Your email address will be destroyed after the study has been completed. Relevant data collected during the study, may be looked at by individuals from the Birmingham Women's and Children's NHS Foundation Trust, the University of Birmingham, or from regulatory authorities, where it is relevant to your taking part in this research.

General Data Protection Regulations (GDPR) for health and care research

The University of Birmingham is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Birmingham will keep identifiable information about you for 10 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how your information is used at
https://www.birmingham.ac.uk/privacy/index.aspx

Birmingham Women's and Children's NHS Foundation Trust will use your name, hospital number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from The University of Birmingham and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Birmingham Women's and Children's NHS Foundation Trust will pass these details to The University of Birmingham along with the information collected from you and your medical records. The only people in The University of Birmingham who will have access to information that identifies you will be people who need to contact you to obtain follow-up information or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, hospital number or contact details.

Birmingham Women's and Children's NHS Foundation Trust will keep identifiable information about you from this study for 10 years after the study has finished.

The University of Birmingham will collect information about you for this research study from your patient records. This information will include your name, hospital number, contact details and health information, which is regarded as a special category of information. We will use this information to obtain follow-up information where necessary.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

Do I have any rights to the research?

If you participate in our research, you will donate any samples as an altruistic gift to help us to find out why miscarriage happens and potentially to find ways to help avoid or treat it in the future. You will not be entitled to restrict the particular questions that the research seeks to answer, and in the unlikely event that any findings are patented for commercial application then you will not be paid.

What are the benefits from participating in the study?

If you choose to participate in this study you will receive a more detailed scan called a Hysterosalpingo-contrast-sonogram or HyCoSy and extra screening for infection. If a hydrosalpinx is found on scan you may be offered surgery to treat this which may reduce the risk of suffering a further miscarriage in the future. You will be contributing towards the knowledge of the causes of recurrent miscarriage which may help develop future treatments for this condition.

What are the disadvantages of participating in the study?

Apart from the inconvenience of having an additional test for infection, a more detailed internal ultrasound scan called a HyCoSy, the time for 2 telephone/ face to face/ email consultations and any emotional distress caused by recalling any traumatic events there are no disadvantages of participating in this study. It is current normal practice during investigations for recurrent miscarriage to have an internal ultrasound scan. There is no additional risk from this scan to yourself when compared to current practices during fertility investigations.

What will happen at the end of the study?

We anticipate that this research study will run for 3 years. As and when our research findings are published, we will make them available on the Tommy's website and you may be emailed a summary of the findings if you provide an email address.

Who is organising and funding the research?

Within Birmingham Women's Hospital this research is coordinated by Tommy's National Centre for Miscarriage Research. The research is funded by Tommy's charity, who wish to advance work in this area. Tommy's charity makes independent choices about which research projects to support, and has chosen to support our early pregnancy research. The Tommy's National Centre for Miscarriage Research is a collaboration between the University of Birmingham, University of Warwick and Imperial College London and their associated NHS hospitals. The charity insists that any funded project has received appropriate ethical consideration.

Who is providing the insurance for the research?

The study is sponsored by The University of Birmingham (RG_17-150). The University purchases Clinical Trials Cover, which provides automatic insurance cover for all Clinical Trials including those where the University accepts responsibility as sponsor, for any harm that comes about due to the University's, or its staff's negligence in relation to the design or management of the trial. In some cases, cover can also be provided in the case of non-negligent harm to participants.

Who has reviewed the study?

All research projects must be approved by a Research Ethics Committee. This project has also been peer reviewed by Prof T J Clark – Honorary Professor of Gynaecology at Birmingham Women's Hospital.

For further information

You can discuss the details of this study with:
Professor Arri Coomarasamy (Professor of Gynaecology at University of Birmingham),
Dr Jay Ghosh (Clinical Research Fellow and Registrar in Obstetrics and Gynaecology)
Contact:
Email:

For emotional/ bereavement support

Our specialist bereavement support team are here to support you and your family through difficult times. They offer a variety of facilities to help you to cope with loss. You can telephone the bereavement team on 0121 623 6882 or 07814 20 84 35. Their office hours are 8.30am to 4.30pm Monday to Friday. Outside of these hours you can leave a message and they will get back to you as soon as possible. Other organisations that you may find helpful include:

Tommy's
www.tommys.org
Miscarriage Association
www.miscarriageassociation.org.uk

Concerns & Complaints

If you have any concerns or complaints about this study which cannot be answered by contacting either the mobile or email address above, you can contact the Patient Advice and Liaison Service or sponsor's representative whose contact details are listed below.

Patient Advice and Liaison Service (PALS) for Birmingham Women's Hospital

The PALS office can be found in the front of the house area of the hospital.
Tel - 0121 627 2747
Website - http://www.bwnft.nhs.uk/patients-visitors/patient-advice-and-information-centre

Sponsor's Representative
Mr David Law – Head of Research Support Group for the University of Birmingham
Tel -
Email - researchgovernance@contacts.bham.ac.uk

Appendix 14: Patient consent form v1.2 for "The role of hydrosalpinx in recurrent miscarriage"







The Role of Hydrosalpinx in Recurrent Miscarriage Study

Participant Consent Form

Please initial each box to con irm consent

confirm that have read and understand the information sheet (v1 2 8-Aug-2018) for the above study have had the opportunity to consider the information ask questions and these have been answered satisfactorily	☐
understand that my participation is voluntary and that if take part am free to withdraw at any time without giving a reason and without my treatment or legal rights being affected	☐
understand that if withdraw from the study anonymised information already collected about me to the stage of withdrawal may be used in the final analysis	☐
understand what is involved in the study and will be happy to take a self-taken vulvo-vaginal swab and a hysterosalpingo-contrast-sonogram which will involve a transvaginal ultrasound scan	☐
understand that will be contacted via telephone or email in approximately 6 and 12 months' time to ask me about any future pregnancies miscarriages ectopic pregnancies live births and stillbirths	☐
understand that my results as well as my patient records will be viewed by the research team who are outside of my direct care team as well as my direct care team and that all clinical information will be kept confidential	☐
understand that if subsequently seek treatment related to early pregnancy or obstetric problems in another local hospital that the research team may obtain information relevant to the study from my patient records at that hospital	☐
give permission for my GP to be contacted and informed of my participation in this study	☐
understand and agree that the research team may wish to contact me via telephone email or letter in order to gather or distribute further information if required	☐
understand that relevant data collected during the study may be looked at by individuals from the Birmingham Women's and Children's NHS Foundation Trust the University of Birmingham from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research give permission for these individuals to have access to this data	☐
agree to participate in the role of hydrosalpinx in recurrent miscarriage study	☐

.....	.....	.....
Name of Patient in Block Capitals	Date	Signature
.....	.....	.....
Name of Person taking consent	Date	Signature

Study Number ..... Contact Telephone Number

Email Address.....

IRAS ID: 232650, UoB Research Governance Reference Number: RG_17-150
Participant consent form v1.2, 8-Aug-2018

Appendix 15: Confirmation NHS Health Research Authority approval for amendment for "The role of hydrosalpinx in recurrent miscarriage"

IRAS Project ID 232650. HRA Approval for the Amendment

hra.amendments@nhs.net <noreply@harp.org.uk>

Mon 17/12/2018 16:28

To

Cc

Dear Prof Coomarasamy,

IRAS Project ID:	232650
Short Study Title:	The role of hydrosalpinx in recurrent miscarriage
Amendment No./Sponsor Ref:	1
Amendment Date:	08 August 2018
Amendment Type:	Substantial Non-CTIMP

I am pleased to confirm **HRA and HCRW Approval** for the above referenced amendment.

You should implement this amendment at NHS organisations in England and Wales, in line with the conditions outlined in your categorisation email.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

Please contact [hra.amendments@nhs.net]hra.amendments@nhs.net for any queries relating to the assessment of this amendment.

Kind regards

Mrs Alka Bhayani
Amendments Coordinator
Health Research Authority
Ground Floor | Skipton House | 80 London Road | London | SE1 6LH

E.hra.amendments@nhs.net
W. www.hra.nhs.uk

Sign up to receive our newsletter HRA Latest.

Appendix 16: Confirmation of registration with Clinicaltrial.gov for "The role of hydrosalpinx in recurrent miscarriage"

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: October 9, 2018

ClinicalTrials.gov ID: [Not yet assigned]

Study Identification

Unique Protocol ID:	IRAS ID 232650
Brief Title:	The Role of Hydrosalpinx in Recurrent Miscarriage
Official Title:	The Role of Hydrosalpinx in Recurrent Miscarriage
Secondary IDs:	

Study Status

Record Verification:	October 2018
Overall Status:	Recruiting
Study Start:	February 28, 2018 [Actual]
Primary Completion:	February 2020 [Anticipated]
Study Completion:	July 2020 [Anticipated]

Sponsor/Collaborators

Sponsor:	University of Birmingham
Responsible Party:	Principal Investigator Investigator: Dr Jayasish Ghosh [jghosh] Official Title: Principal Investigator Affiliation: University of Birmingham
Collaborators:	Tommy's Charity

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: IRAS ID 232650 Board Name: West Midlands Edgbaston Research Ethics Committee Board Affiliation: NHS Health Research Authority Phone: 0207 104 8104 Email: NRESCommittee.westmidlands-edgbaston@nhs.net Address: Nottingham HRA
Data Monitoring:	No

FDA Regulated Intervention: No

Study Description

Brief Summary: Miscarriage affects one in five pregnancies and little progress has been made in understanding and treating this distressing condition. C. trachomatis is the most common sexually transmitted infection in the UK. C. trachomatis infection can have serious health consequences, including fallopian tube damage. Untreated C. trachomatis infection and tubal damage have been associated with miscarriage and adverse pregnancy outcomes such as preterm birth, low birth weight and stillbirth. A cohort study is needed to establish the prevalence of tubal disease in women with recurrent miscarriages. HyCoSy will be performed to identify tubal disease and establish the magnitude of the problem in the recurrent miscarriage population. The prognosis of tubal disease on miscarriage and other obstetric outcomes, and the role of medical interventions such as tubal surgery (to treat hydrosalpinx) on reducing miscarriage and adverse obstetric outcomes will also be studied.

Objectives

1. Establish the prevalence of hydrosalpinx in the recurrent miscarriage population.
2. Establish the prognosis of women diagnosed with recurrent miscarriage with concurrent hydrosalpinx.
3. Explore the role of tubal surgery for improving reproductive outcomes in women with recurrent miscarriage population and hydrosalpinx.

Detailed Description:

Conditions

Conditions: Abortion, Spontaneous
Miscarriage, Recurrent
Hydrosalpinx

Keywords:

Study Design

Study Type: Observational

Observational Study Model: Cohort

Time Perspective: Prospective

Biospecimen Retention: None Retained

Biospecimen Description:

Enrollment: 203 [Anticipated]

Number of Groups/Cohorts: 3

Groups and Interventions

Groups/Cohorts	Interventions
Women with recurrent miscarriage and no hydrosalpinx	Diagnostic Test: Hysterosalpingo-contrast-sonogram

Groups/Cohorts	Interventions
	A contrast ultrasound scan to examine fallopian tube pathology and blockage
Women with recurrent miscarriage and concurrent hydrosalpinx	Diagnostic Test: Hysterosalpingo-contrast-sonogram A contrast ultrasound scan to examine fallopian tube pathology and blockage
Women with recurrent miscarriage and treated hydrosalpinx	Diagnostic Test: Hysterosalpingo-contrast-sonogram A contrast ultrasound scan to examine fallopian tube pathology and blockage

Outcome Measures

Primary Outcome Measure:

1. Hydrosalpinx
   The presence or absence of tubal blockage and hydrosalpinx

   [Time Frame: 12 months]

Secondary Outcome Measure:

2. Miscarriage
   The loss of a pregnancy below 24 completed week of gestation

   [Time Frame: 12 months]

Eligibility

Study Population: Women who have suffered from 2 or more pregnancy losses

Sampling Method: Non-Probability Sample

Minimum Age: 18 Years

Maximum Age: 45 Years

Sex: Female

Gender Based: Yes
Must be genetically female as must have suffered from previous pregnancy losses

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Age 18-45
- Women diagnosed with recurrent miscarriage i.e. 2 or more miscarriages
- Ability to give informed consent

Exclusion Criteria:

- Allergy to contrast media used for Hysterosalpingo-contrast-sonogram
- Allergy to sonographic gel used for ultrasound scanning
- Anatomical anomaly meaning transvaginal ultrasound scan not possible
- Stenosed/occluded cervix meaning contrast media unable to be introduced via cervix
- Inability to give informed consent

- Pregnant at the time of recruitment
- Declined recruitment

Contacts/Locations

Central Contact Person: Jayasish Ghosh, MBBS

Central Contact Backup:

Study Officials:

Locations: United Kingdom
Birmingham Womens Hospital
[Recruiting]
Birmingham, West Midands, United Kingdom, B15 2TG
Contact:

IPDSharing

Plan to Share IPD: No

References

Citations:

Links:

Available IPD/Information:

Documents

Study Protocol
Document Date: December 28, 2017
Uploaded: 10/09/2018 08:45

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

Appendix 17: Confirmation of approval from NIHR CRN as portfolio study for "The role of hydrosalpinx in recurrent miscarriage"

FW: For Action: CPMS ID [36974] – Completion of your Central Portfolio Management System (CPMS) Record

Arri Coomarasam

Fri 28/09/2018 09:55

To

Cc

1 attachment

Portfolio Study Details Request Form final with narrative docx;

From: **On Behalf Of** NIHR Clinical Research Network (Portfolio)
Sent: 28 September 2018 09:29
To: Arri Coomarasamy (Institute of Metabolism and Systems Research)
Subject: For Action: CPMS ID [36974] – Completion of your Central Portfolio Management System (CPMS) Record

Dear Dr Coomarasamy,

RE: IRAS 232650, CPMS 36974
The role of hydrosalpinx in recurrent miscarriage

Your study has been deemed eligible to receive NIHR Clinical Research Network (CRN) support and a record has been created for your study in the NIHR Central Portfolio Management System (CPMS). Your study record has been populated from information you provided as part of the eligibility and HRA Approval process (i.e. NHS R&D Form, protocol and grant award letter). However, in order to complete the registration of your study on the NIHR CRN Portfolio some additional information is required.

Please could you ensure that you, or your designated Study Coordinator, complete and return the attached **Study Details Form** within **five working days** of the date of this email.

We require this information in order to complete your study record. This will ensure the visibility of your study across the Clinical Research Network to effectively support the set up and delivery of your study.

Kind regards,

Tom

NIHR Clinical Research Network (Portfolio)



e. crncc.portfolioa@nihr.ac.uk
a. 21 Queen Street, Leeds, LS1 2TW

We would really appreciate you taking 5-10 minutes to tell us about your experience of working with us. Providing this feedback will help us to understand how we can improve our service to you. Please click here to complete our survey: https://www.surveymonkey.co.uk/r/studysupportservice

Confidential information may be contained in this message.If you are not the intended recipient, any reading, printing, storage, disclosure, copying or any other action taken in respect of this e-mail is prohibited and may be unlawful. If you are not the intended recipient, please notify the sender immediately by using the reply function and then permanently delete what you have received.

END