

Methods for managing miscarriage: a network meta-analysis

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Methods for managing miscarriage: a network meta-analysis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The objectives of this review are:

- to estimate the relative effectiveness and safety profiles for methods of management of miscarriage;
- to provide a ranking of the available methods according to their effectiveness and safety profile.

BACKGROUND

Description of the condition

Miscarriage is the most common cause of pregnancy loss. An estimated 15% to 20% of pregnancies will end in miscarriage, with 25% of women experiencing a miscarriage in their lifetime (Alberman 1992). This can have an emotional and a physical impact on both women and their partners that can last well beyond the pregnancy (Conway 2000; Geller 2001; Neugebauer 1997).

Miscarriage is generally defined as the spontaneous loss of a pregnancy 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-income countries (MBRRACE-UK 2016).

Description of the intervention

Miscarriage can be managed expectantly, medically (with tablets) or surgically. Although historically miscarriages were often treated with a surgical procedure, women now have the options of expectant or medical management. However, there is uncertainty about their relative effectiveness and risks.

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 adverse events, such as anaesthetic complications, infection, uterine perforation and Asherman's syndrome. Suction curettage (electrical or manual vacuum aspiration) has replaced sharp curettage in high-income countries and has a well-documented safety profile and is included in the essential surgical equipment by the World Health Organization (WHO) for obstetric care at first referral level (WHO 2009). Even so, it is less commonly used in low-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.

Medical methods of management of miscarriage include various agents. Misoprostol is 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). However, it is associated with side-effects such as diarrhoea, abdominal pain, nausea and vomiting, shivering and pyrexia (Tunçalp 2012). 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, without associated pain and bleeding (also known as early fetal demise, delayed miscarriage or silent miscarriage). In women with incomplete miscarriage with a diagnosed non-viable pregnancy in which bleeding has begun, but some pregnancy tissue remains in the uterus, the anti-progesterone effect of mifepristone is considered less useful and treatment is aimed to stimulate uterine contractility often with misoprostol alone.

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 (Kim 2017; Nanda 2012; Tunçalp 2010; Webber 2015). However, a standard pairwise meta-analysis can only compare two drugs 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 comparisons about 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. Network meta-analysis can additionally be used to identify gaps in the evidence base.

OBJECTIVES

The objectives of this review are:

- to estimate the relative effectiveness and safety profiles for methods of management of miscarriage;
- to provide a ranking of the available methods according to their effectiveness and safety profile.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled comparisons or cluster trials that assess the effectiveness or safety of methods for miscarriage management. Quasi-randomised trials will be eligible for inclusion. We will exclude non-randomised trials.

Types of participants

We will consider for inclusion all studies that include women who are being treated for early miscarriage (pregnancy loss at less than 14 weeks), diagnosed by ultrasound or clinically alone. We will include women with both missed and incomplete miscarriage. Also we will consider for inclusion studies conducted in all settings. We will include all women regardless of age.

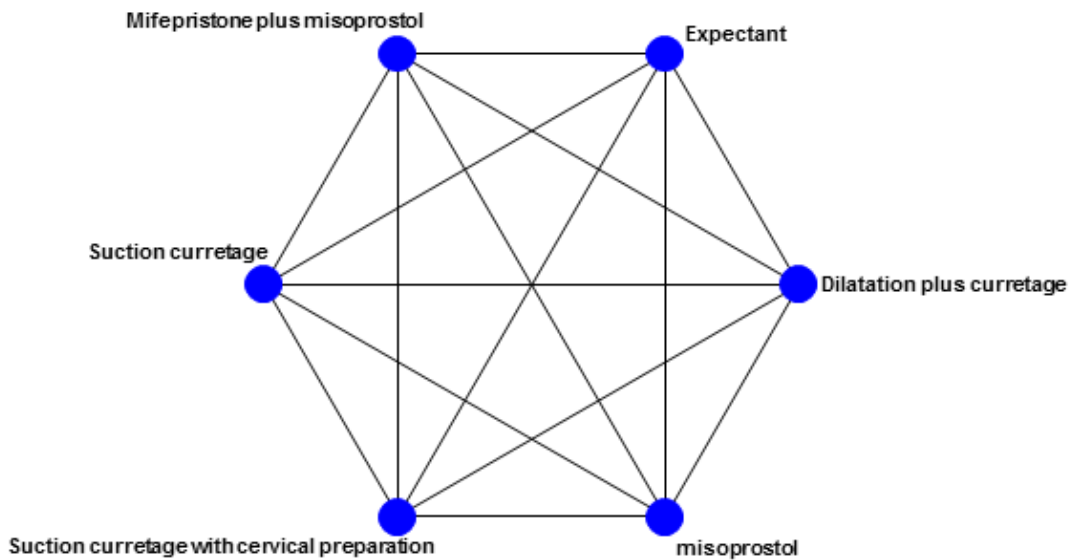
Types of interventions

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.

If we identify interventions in the included studies of which we are not aware, we will consider including them after we assess their comparability with those interventions named above.

We will stratify all interventions according to the gestation, type of miscarriage and drug strategy (dose, route or regimen), to detect inequalities that could affect comparative effectiveness. We will include regimens irrespective of their dose as long as it is in the therapeutic range. Multi-arm trials that compare different dosages, regimens or routes of one drug, but also compare those versus another drug, will be included. We will merge the intervention arms of different dosages, regimens or routes of the same drug together for the global analysis of all outcomes and will treat them as separate independent comparisons only for the relevant subgroup analysis according to dosage, regimen and route of drug administration, while taking into account the correlation between the comparisons. We will also include trials that compare exclusively different dosages, regimens or routes of administration of the same drug. The review will be restricted to studies that evaluate drugs administered by healthcare professionals (Figure 1).

Figure 1. Network plot for management of miscarriage.



We will code the comparisons within a study as follows:

- expectant = any management that does not involve any surgical or medical treatment;
- suction curettage = any surgical management that involves a suction curette without any cervical preparation agents;
- suction curettage with cervical preparation = any surgical management that involves a suction curette with cervical

preparation agents;

- dilatation plus sharp 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 alone = any medical management with the use of misoprostol alone at any dose, route or regime.

Participants in the network could in principle be randomised to any of the methods being compared. For example, a woman with an early miscarriage could be equally likely to be randomised to manual vacuum aspiration, dilatation plus curettage, misoprostol, suction curettage, cervical preparation plus suction curettage, mifepristone plus misoprostol or expectant management.

We will also 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, if data exist and will be part of a subgroup analysis. We also aim 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 if sufficient data exist.

Types of outcome measures

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;
- 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/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 will search Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist.

The Register is a database that contains over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate the Cochrane 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 to the editorial information about [Cochrane Pregnancy and Childbirth](#) in the Cochrane Library and select the 'Specialized Register' section from the options on the left side of the screen.

In brief, the 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. handsearches 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.

Two people screen the search results 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 Cochrane 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 will be fully accounted for in the relevant review sections (included studies, excluded studies, studies awaiting classification or ongoing studies). In addition, we will search [ClinicalTrials.gov](#) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports using the terms listed in [Appendix 1](#).

Searching other resources

We will retrieve additional relevant references cited in papers identified through the above search strategy. We will search for the full texts of studies identified as abstracts. We will seek information from primary authors to investigate whether these studies meet eligibility criteria, and to obtain outcome and study data. If this is

not possible, we will only include abstracts if we can extract sufficient information to satisfy our eligibility criteria and the study authors report the outcomes of interest. Trials that compare at least two of the drugs are eligible and we shall search for all possible comparisons formed by the drugs of interest.

We will search the reference lists of retrieved studies.

We will not apply any language or date restrictions.

Data collection and analysis

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

Selection of studies

Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreements through discussion or, if required, we will consult a third review author. We will create a PRISMA study flow diagram to map out the number of records identified, included and excluded. We will list all studies excluded after full-text assessment and their reasons for exclusion in a 'Characteristics of excluded studies' table.

Data extraction and management

We will design an electronic form in Microsoft Access software to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third review author. We will enter data into Review Manager 5 (RevMan 5) software and will check for accuracy (RevMan 2014). When information regarding any of the above is unclear, we will attempt to contact the authors of the original reports to provide further details.

We will extract the following data.

Outcome data

From each included study we will extract the number of participants, the parity of participants, along with the inclusion and exclusion criteria. We will also extract the interventions being compared including the healthcare setting and type of anaesthesia used, and their respective primary and secondary outcomes. We will extract all relevant arm level data (e.g. number of events and number of participants for binary outcomes).

Data on potential effect modifiers

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

- gestational age (\geq nine weeks versus greater than nine weeks of gestation);
- type of miscarriage (incomplete versus missed miscarriage);
- dosage, regimen, and route of drug administration (sublingual, rectal, oral).

Other data

From each included study we will extract 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

Two review authors will independently assess the risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a third review author.

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

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

We will assess 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 will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

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

We will assess methods used to blind outcome assessment as at:

- low, high or unclear risk of bias.

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

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will 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 is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess 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 will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is 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 are 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 will describe for each included study any important concerns we have about other possible sources of bias.

We will assess 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 will make 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 will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses (see the 'Sensitivity analysis' section).

Measures of treatment effect

For dichotomous data, we will present results as a summary risk ratio with 95% confidence intervals (CIs). For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use 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, we will, where possible, account for the within-patient correlation between baseline and post-miscarriage estimates (Dias 2013).

Relative treatment ranking

We will also estimate the ranking probabilities for all treatments of being at each possible rank for each intervention (conditional on the model and specified vague priors). Then we will obtain a

treatment hierarchy using the surface under the cumulative ranking curve (SUCRA). SUCRA can also be expressed as a percentage of effectiveness or side-effects of a treatment that would be ranked first without uncertainty. For primary outcomes, we will assess the robustness of these findings in sensitivity analysis by considering estimates of mean rank with 95% CIs. We will also present the 'Summary of findings' tables using [GRADEpro](#) Guideline Development Tool (GDT) software for each outcome. In the 'Summary of findings' tables, we will follow the approach suggested by [Schünemann 2009](#) and [Puhan 2014](#).

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. Where necessary, we will adjust their standard errors using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 16.3.4 or 16.3.6) 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 use ICC values from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials are not eligible for this review.

Multi-arm trials

We will include multi-arm trials and we will account for the correlation between the effect sizes in the network meta-analysis. We will treat multi-arm studies as multiple independent comparisons in pairwise meta-analyses.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

We will impute missing standard deviations and errors using standard techniques where possible ([Higgins 2011](#)).

For all outcomes, we will perform analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and we will analyse 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 will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity

To evaluate the presence of clinical heterogeneity, we will generate descriptive statistics for trial and study population characteristics across all eligible trials that compare each pair of interventions. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics.

Assessment of transitivity across treatment comparisons

We will assess 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:

- 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 to in misoprostol versus suction curettage trials and in misoprostol versus mifepristone plus misoprostol trials);
- all pairwise comparisons do not differ with respect to the distribution of effect modifiers (e.g. the design and study characteristics of suction curettage versus misoprostol trials are similar to misoprostol versus mifepristone plus misoprostol trials).

We will evaluate the assumption of transitivity epidemiologically by comparing the clinical and methodological characteristics of sets of studies grouped by treatment comparisons.

Assessment of statistical heterogeneity and inconsistency

Assumptions when estimating the heterogeneity

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

Measures and tests for heterogeneity

We will assess 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.

We will base the assessment of statistical heterogeneity in the entire network on the magnitude of the heterogeneity variance parameter (τ^2) estimated from the network meta-analysis models. For dichotomous outcomes we will compare the magnitude of the heterogeneity variance with the empirical distribution as derived by Turner (Turner 2012). We will also estimate a total I^2 statistic value for heterogeneity in the network as described elsewhere.

Assessment of statistical inconsistency

The statistical agreement between the various sources of evidence in a network of interventions (consistency) will be 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 will use 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). 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 will assume a common heterogeneity estimate within each loop.

Global approaches for evaluating inconsistency

To check the assumption of consistency in the entire network we will use the “design-by-treatment” model as described by Higgins 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 will infer about the presence of inconsistency from any source in the entire network based on a Chi^2 test. We will perform the design-by-treatment model in STATA using the `mvmeta` command (StataCorp 2011).

Inconsistency and heterogeneity are interweaved; to distinguish between these two sources of variability we will employ 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

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we will aim 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 are 10 or more studies in the network meta-analysis, we will use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies) and account for the fact that studies estimate effects for different comparisons.

Data synthesis

Methods for direct treatment comparisons

We will perform standard pairwise meta-analyses using a random-effects in the presence of substantial heterogeneity or fixed-effect model in STATA for every treatment comparison (DerSimonian 1986).

Methods for indirect and mixed comparisons

We will perform network meta-analysis using a random-effects model in STATA with the `mvmeta` command within the network suite of commands for network meta-analysis (White 2015), and other STATA commands for visualising and reporting results in network meta-analysis (Chaimani 2015).

Subgroup analysis and investigation of heterogeneity

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.

- gestational age (\geq 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.

Sensitivity analysis

For the primary outcomes we will perform sensitivity analysis for the following:

- overall quality 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.

'Summary of findings' table

We will assess the quality of the evidence using the GRADE approach as outlined in the [GRADE handbook](#) in order to assess the quality of the body of evidence relating to the primary outcomes for all comparisons including subgroups by type of miscarriage (missed versus incomplete miscarriage):

- complete miscarriage;
- composite outcome of death or serious complications.

In order to create 'Summary of findings' tables, we will use [GRADEpro](#) GDT, to import data from RevMan 5 ([RevMan 2014](#)). We will produce a summary of the intervention effect and a measure of quality for each of the above outcomes using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. We will follow the

approach suggested by [Puhan 2014](#) and [Schünemann 2009](#), and provide estimates from the network meta-analysis.

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REFERENCES

Additional references

Alberman 1992

Alberman E. Spontaneous abortions: epidemiology. In: Stabile I, Grudzinkas JG, Chard T editor(s). *Spontaneous Abortion: Diagnosis and Treatment*. London: Springer-Verlag, 1992:9–20.

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.

Chaimani 2015

Chaimani A, Salanti G. Visualizing assumptions and results in network meta-analysis: the network graphs package. *Stata Journal* 2015;**15**:4.

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 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 JPT, 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. [DOI: 10.1002/14651858.CD007223.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. [DOI: 10.1002/14651858.CD003518.pub3]

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.

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.

Schaff 2005

Schaff EA, DiCenzo R, Fielding SL. Comparison of misoprostol plasma concentrations following buccal and

sublingual administration. *Contraception* 2005;**71**(1): 22–25.

Schünemann 2009

Schünemann HJ. GRADE: from grading the evidence to developing recommendations. A description of the system and a proposal regarding the transferability of the results of clinical research to clinical practice [GRADE: Von der Evidenz zur Empfehlung. Beschreibung des Systems und Lösungsbeitrag zur Übertragbarkeit von Studienergebnissen]. *Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen* 2009;**103**(6):391–400. [PUBMED: 19839216]

Shiers 2003

Shiers C. Abnormalities of early pregnancy. *Myles' Textbook for Midwives*. 14th Edition. Churchill Livingstone, 2003.

StataCorp 2011 [Computer program]

StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp, 2011.

Tunçalp 2010

Tunçalp Ö, Gülmezoglu AM, Souza JP. Surgical procedures for evacuating incomplete miscarriage. *Cochrane Database of Systematic Reviews* 2010, Issue 9. [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. [DOI: 10.1002/14651858.CD000494.pub4]

Turner 2012

Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JPT. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012;**41**(3):818–827.

Webber 2015

Webber K, Grivell RM. Cervical ripening before first trimester surgical evacuation for non-viable pregnancy. *Cochrane Database of Systematic Reviews* 2015, Issue 11. [DOI: 10.1002/14651858.CD009954.pub2]

White 2015

White IR. Network meta-analysis. *Stata Journal* 2015;**15**:4.

WHO 2009

World Health Organisation 2009. Integrated management for emergency and essential surgical care (IMEESC) toolkit. www.who.int/surgery/publications/imeesc/en/ (accessed 10 March 2017).

* Indicates the major publication for the study

APPENDICES

Appendix I. 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

CONTRIBUTIONS OF AUTHORS

Ioannis D Gallos (IDG) and Arri Coomarasamy (AC) conceived the idea for this protocol. IDG, AC, Malcolm J Price (MP), Abey Eapen (AE), Aurelio Tobias (AT), Jonathan J Deeks (JJD), Özge Tunçalp (OT), A Metin Gülmezoglu (AMG) designed the meta-analysis. MP, JZ, AT and JJD provided statistical advice and input. IDG drafted the protocol. Helen M Williams (HMW), MP, AE, Mary M Eyo (MME), AT, OT, AMG, AC and JJD reviewed the protocol and provided critical feedback. IDG is the guarantor for this review.

DECLARATIONS OF INTEREST

IDG, HMW, MP, AE, AT, OT, AMG and AC have no known conflicts of interest.

JJD is a co-applicant to the UK National Institute for Health Research HTA Project Award 14/139/17 entitled “Uterotonic drugs for preventing postpartum haemorrhage: a network meta-analysis and cost-effectiveness analysis”.

MME, as an academic clinical fellow, receives an allowance of GBP 1000 per annum, which may be used for the development of presentations that arise from this project. However, there are no financial relationships with any organisations that might have an interest in the submitted work and no other relationships or activities that could appear to influence the submitted work.

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