Management of first-trimester miscarriage: a systematic review and network meta-analysis

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Abstract

Background: First-trimester miscarriage affects up to a quarter of women worldwide. With many competing treatment options available, there is a need for a comprehensive evidence synthesis.

Objectives and rationale: We conducted a systematic review and network meta-analysis to assess the effectiveness and safety of treatment options for first-trimester miscarriage: expectant management (EXP), sharp dilation and curettage (D+C), electric vacuum aspiration (EVAC), manual vacuum aspiration (MVA), misoprostol alone (MISO), mifepristone+misoprostol (MIFE+MISO) and misoprostol plus electric vacuum aspiration (MISO+EVAC).

Search methods: We searched MEDLINE, Embase, CINAHL, AMED and Cochrane Library from inception till June 2018. We included randomised trials of women with first-trimester miscarriage (<14 weeks gestation) and conducted a network meta-analysis generating both direct and mixed evidence on the effectiveness and side effects of available treatment options. The primary outcome was complete evacuation of products of conception. We assessed the risk of bias and the global network inconsistency. We compared the surface under the cumulative ranking curve (SUCRA) for each treatment.

Outcomes: A total of 46 trials (9250 women) were included. The quality of included studies was overall moderate with some studies demonstrating a high risk of bias. We detected unexplained inconsistency in evidence loops involving MIFE+MISO and adjusted for it. EXP had lower effectiveness compared to other treatment options. The effectiveness of medical treatments was similar compared to surgery. Mixed evidence of low confidence suggests increased effectiveness for MIFE+MISO compared to MISO alone (RR 1.49, 95% CI 1.09-2.03). Side effects were similar among all options. Fewer women needed analgesia following EVAC compared to MISO (RR for MISO 0.43, 95% CI 0.27-0.68) and in the EXP group

compared to EVAC (RR 2.07, 95% CI 1.25-3.41). MVA had higher ranking (low likelihood) for post-treatment infection and serious complications (SUCRA 87.6%, 79.2%respectively) with the highest likelihood for post-treatment satisfaction (SUCRA 98%).

Wider implications: Medical treatments for first-trimester miscarriage have similar effectiveness and side effects compared to surgery. The addition of MIFE could increase the effectiveness of MISO and reduce side effects, although evidence is limited due to inconsistency. EXP has lower effectiveness compared to other treatment options.

Systematic review registration: Prospero CRD42016048920

Keywords: miscarriage, pregnancy loss, first trimester, effectiveness, woman, systematic review, network meta-analysis.

Introduction

First trimester miscarriage, the most common time of pregnancy loss, is estimated to affect up to a quarter of pregnant women in their lifetime (Wang *et al.*, 2003). Miscarriage can lead to significant clinical and emotional morbidity, affecting the couples' quality of life (Jurkovic *et al.*, 2013). Providing patient-centred care can help to reduce the psychological squelae associated with miscarriage (van den Berg *et al.*, 2017) such as increased anxiety, depression, grief and low self-esteem (Frost and Condon, 1996; Swanson *et al.*, 2009). The burden of miscarriage on healthcare resources is significant, leading to over 50,000 hospital admissions annually in the UK (The National Institute for Health and Care Excellence, 2012), with a similar impact in other developed countries (Queensland Clinical Guidelines, 2015; The American College of Obstetricians andGynecologists, 2015).

Various treatment options exist for couples experiencing first-trimester miscarriage; these are broadly categorised into expectant, medical and surgical groups (Trinder *et al.*, 2006). The wide use of less invasive treatments such as prostaglandins and manual vacuum evacuation could reduce the need for surgical interventions under general anaesthesia and the number of hospital admissions (Jurkovic *et al.*, 2013; Sotiriadis *et al.*, 2005). Misoprostol is currently the most used drug for treating miscarriage, however, there is no consensus on the best dose and route of its administration (Neilson *et al.*, 2013). Combining medical and surgical treatments is common, though evidence to support this practice is imprecise (Fang *et al.*, 2009). Evidence concerning the effectiveness and safety of available treatment options is limited to pairwise comparisons in randomised trials and their meta-analyses (Nanda *et al.*, 2006; Neilson *et al.*, 2013; Sotiriadis *et al.*, 2005; Tunçalp *et al.*, 2010).

There is a need for a comprehensive evidence synthesis to compare the effectiveness and safety of the available treatment options. We conducted a systematic review and a network meta-analysis of randomised trials (comparing different treatments for a particular condition using the estimated effect size from direct and indirect comparisons) (Al Wattar *et al.*, 2017) to assess the effectiveness and side effects of available treatment options for complete evacuation of products of conception in women experiencing first-trimester miscarriage.

Methods

We conducted our systematic review according to a prospectively registered protocol (Prospero CRD42016048920) and reported the findings to comply with the extended PRISMA guidelines (Hutton *et al.*, 2015). The final author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and there are no discrepancies from the planned study protocol.

Search strategy

We searched the following electronic databases for randomised trials comparing any treatment option for first-trimester miscarriage from inception until June 2018 (MEDLINE, Embase, CINAHL, AMED and Cochrane Library). We developed a multi-step search strategy and adjusting it appropriately for each database (not shown). No search filters were applied. We conducted supplementary searches in Google Scholar and Scopus. We manually screened bibliographies of reviewed articles to identify any additional relevant trials. Articles in non-English language were obtained and translated if deemed relevant. We contacted authors for further information when needed, but no unpublished data were included. We reviewed all available systematic reviews on the management of first-trimester miscarriage to identify any additional studies.

Selection criteria and data extraction

We included all randomised trials that evaluated any treatment option in women with first-trimester miscarriage (defined as a spontaneous loss of a non-viable intrauterine pregnancy between 0 and 14 weeks' gestation) (The National Institute for Health and Care Excellence, 2012). Studies that included a combination of two treatment options (e.g. medical plus surgical) were included. Studies with multiple comparison arms were also included. We excluded quasi-randomised studies and those reporting on elective termination of pregnancy. Studies that compared variations of the same treatment in both arms (e.g. misoprostol 400 µg vs misoprostol 600 µg) were reported narratively and excluded from the meta-analysis. Studies that reported on secondary outcomes only were also excluded.

We manually extracted data, using a bespoke electronic tool, on the place of the study, the publication journal, treatment settings, population characteristics, the treatment options evaluated, including its dose and route where applicable, and primary and secondary outcomes. The selection and data extraction processes were conducted in duplicate by two independent reviewers (BHA and NM). Any disagreement was resolved by discussion with a third reviewer (KSK).

Primary and secondary outcomes

Our primary outcome was complete evacuation of products of conception, defined clinically or on ultrasound as an empty uterine cavity without the need for further treatment. Secondary outcomes were: serious complications (defined as a composite of any of the following: uterine perforation, cervical tear, hysterectomy, laparotomy, Asherman's syndrome, and death), need for blood transfusion, post-treatment infection/pelvic inflammatory disease, nausea, vomiting, diarrhoea, fever (>38 ºC with no evidence of infection), patient

satisfaction, mean hospital stay (days), visual analogue pain scores, anxiety, depression and need for analgesia.

Types of treatment for first trimester miscarriage

Treatment options were grouped into five categories: expectant (defined as conservative management with no active intervention including placebo), medical (defined as any medical drug of any dose, route and format to achieve uterine evacuation), placebo (defined as a planned placebo intervention within a trial settings), surgical (defined as any surgical instruments used under general or local anaesthesia to achieve uterine evacuation) and a combination of any medical plus surgical treatment used consecutively. To reduce inconsistency in the network, we combined conservative and placebo treatments under the same label (expectant management). We also excluded uncommon medical drugs that were reported in single studies (e.g. Methotrexate) and reported on them narratively.

Quality assessment of risk of bias

We assessed the risk of bias in all included studies in duplicate by two independent reviewers (BHA and NM) using the Cochrane risk of bias assessment tool (Higgins *et al.*, 2011). This included assessment of the following items: randomisation and sequence generation, allocation concealment, blinding and performance, outcome assessment, completeness of outcome data and selective outcome reporting. Unblinded studies were not penalised in the risk of bias assessment due to the nature of the treatments that makes blinding non-feasible. Quality assessment was performed in duplicate by two independent reviewers.

Statistical analysis

We performed standard pairwise meta-analyses using a random-effects model (Sutton *et al.*, 2000) and network meta-analysis within a frequentist framework with multivariate meta-analysis models (White *et al.*, 2012), exploiting the direct and indirect randomised evidence to determine the relative effects and ranking. We reported on direct evidence (from head to head comparison of treatments) and mixed evidence (combining both direct and indirect evidence from comparison of treatments) using weighted mean difference (WMD) for continuous outcomes and risk ratios (RR) for dichotomous outcomes with 95% confidence intervals (CI). We also computed the probability that each treatment is the most effective, as well as the surface under the cumulative ranking curve (SUCRA) to compare the relative ranking probability of each treatment (Chaimani *et al.*, 2013; Salanti *et al.*, 2011). Providing a cumulative rankogram adjusts for any uncertainty in the relative treatment effect where limited evidence exists (Chaimani *et al.*, 2013). A cumulative rank provides the probability for each treatment to be the best among the rang of available treatment options; the SUCRA is a transformation of the mean rank accounting for the location and variance of available treatment effects to generate a treatment hierarchy (Salanti *et al.*, 2011).

In pairwise meta-analyses, we estimated different heterogeneity variances for each pairwise comparison, using the I^2 index, to capture the percentage of variation that is not due to chance. In the network meta-analysis, we assumed a common estimate for the heterogeneity variance across the different comparisons. To check the assumption of consistency in the entire network, we used the design-by-treatment model (Higgins *et al.*, 2012). In case of whole network inconsistency, we investigated differences between direct and indirect evidence using the loop-specific approach (Bucher *et al.*, 1997), assuming a common heterogeneity estimate within each loop (a loop of evidence exist when numerous trials compare a minimum of three treatments e.g A vs B vs C) (Veroniki *et al.*, 2013). We investigated any detected inconsistency and adjusted for unexplained inconsistency within the

network using established models in STATA (Riley *et al.*, 2017). All analyses were done using STATA statistical software, release 14 (StataCorp, College Station, TX, 2015).(Chaimani *et al.*, 2013; White, 2011; White *et al.*, 2012).

Patient involvement

We did not involve a patient representative in the design of our study. We consulted the James Lind Library and previous Cochrane reviews to identify the primary outcome and other outcomes of interest to stakeholders.

Results

Characteristics of included studies

Our electronic search identified 3648 potentially relevant studies. Of these, we excluded 3523 after reviewing titles and abstracts. The remaining 125 studies were assessed in full. Eleven studies were identified from screening bibliographies and were assessed in full. We excluded 90 studies: five reporting on the use of methotrexate, dinoprestone, mifepreistone alone, laminaria, gemeprost (Autry *et al.*, 1999; Al Inizi and Ezimokhai, 2003; Johnson *et al.*, 1997; Lelaidier *et al.*, 1993), 20 comparing different dosages, routes or formats of misoprostol against each other, 15 non- or quasi-randomised, 16 not meeting the inclusion criteria and 34 not reporting the primary outcome. In total 46 randomised trials reporting on 9250 women were included, of these two were in Portuguese (Holanda *et al.*, 2003; Pereira *et al.*, 2006) and one in Norwegian (Karlsen, Jørn-Hugo; Hjalmar, 2001) (Figure 1).

A third of included trials were conducted in European countries (14/46, 30.4%) and fourteen in Asian countries (14/46, 30.4%). Most studies included a two arms comparison and four included three arms. The median study sample size was 60 (range 12-402). The majority of trials were conducted in tertiary healthcare settings (35/46, 76.1%). One study was conducted

in outpatient settings. Eight were multicentre randomised trials (8/46, 17.3%). Table I provides a summary of the characteristics of included trials.

Risk of bias

The quality of included studies was overall moderate with some studies demonstrating a high risk of bias (Supplementary Figure S1). Nine studies had a high risk of bias for randomisation (9/46, 19.5%) and ten (10/46, 21.7%) had a high risk of bias for allocation concealment. Outcomes assesment (i.e. attrition) was judged to have a high risk of bias in six studies, and was inadequate in 15 studies (15/46, 32.6%) but good in 25 studies (25/41, 60.9%). Six studies had a high risk of bias for detection (i.e. selective reporting) (6/46, 13%) and 14 had a high risk of bias in outcomes reporting (i.e. incomplete data) (14/46, 30.4%). Conflict of interest was declared as not present in only seven studies (7/46, 15.2%) and was not reported on in the remaining studies. Only four studies were double blinded and these were studies comparing medical treatments to placebo (3/46, 6%) (Bagratee *et al.*, 2004; Blohm *et al.*, 2005; Lister *et al.*, 2005; Sinha *et al.*, 2018). A summary of risk of bias assessment on included trials is provided in Supplementary Table SII.

Primary outcome

Our network for the primary outcome included 46 randomised trials (9250 women) comparing seven treatment options: expectant management (EXP)(19 trials, 1587 women), sharp dilation and curettage (D+C)(5 trials, 247 women) , electric vacuum aspiration under general anaesthesia (EVAC)(19 trials, 1766 women), manual vacuum aspiration under local anaesthesia (MVA)(12 trials, 1671 women), misoprostol alone (MISO)(32 trials, 3017 women), mifepristone + misoprostol (MIFE+MISO)(9 trials, 932 women), sequential

misoprostol + electric vacuum aspiration under general anaesthesia (MISO+EVAC)(1 trial, 30 women) (Figure 2).

Both direct and mixed evidence supported the overall inferiority of EXP compared to most treatment options for achieving complete evacuation of products of conception (EXP vs MISO RR 0.76, 95% CI 0.65-0.89; EXP vs EVAC RR 0.68, 95% CI 0.59-0.79; EXP vs D+C RR 0.73, 95% CI 0.57-0.94; MISO+EVAC vs EXP RR 1.35, 95% CI 1.10-1.66; MVA vs EXP RR 1.46, 95% CI 1.19-1.79) (Figure 3). All surgical treatments (MVA, EVAC and D+C) demonstrated similar effectiveness for achieving the primary outcome. This was also the case when comparing MISO against each of the surgical treatment options (MVA vs MISO RR 1.10, 95% CI 0.92-1.33; EVAC vs MISO RR 1.11, 95% CI 0.97-1.27; D+C vs MISO RR 1.03, 95% CI 0.82-1.30). Direct evidence on the use of MISO+EVAC was drawn from one trial only (MISO+EVAC vs MISO, RR 2.86, 95% CI 1.45-5.64; data not shown) and mixed evidence supports its superiority only over EXP (RR 1.35, 95% CI 1.10-1.66). Mixed evidence did not support the use of MIFE+MISO compared to using MISO alone to increase effectiveness (RR 1.43, 95% CI 0.87-2.36). However, we detected significant inconsistency between direct and mixed evidence for MISO vs MISO+EVAC; EVAC vs MISO; EVAC vs EXP; EVAC vs MIFE+MISO and EXP vs MISO (Supplementary Table SI). The overall by network inconsistency analysis was significant at p=0.003. Adjusting for inconsistency, mixed evidence favoured the addition of MIFE to MISO to improve effectiveness (MIFE+MISO vs MISO RR 1.49, 95% CI 1.09-2.03) in contrast to MISO+EVAC vs MISO (RR 0.63, 95% CI 0.51-0.79) (Supplementary Figure S3).

The surface under the cumulative ranking curve for treatment effectiveness was highest for MIFE+MISO (SUCRA 89.3%) followed by EVAC (SUCRA 76.2%). EXP was ranked as the least effective treatment (SUCRA 24%) (Figure 4). Visual analysis of our funnel plot

demonstrates a reasonable distribution of effect size with limited evidence of small study effect (Supplementary Figure S4).

Secondary outcomes

Meta-analysis of mixed evidence demonstrated no difference for any of the following outcomes between medical and surgical treatment options: need for blood transfusion, post-treatment infection, serious complications, diarrhoea, vomiting, nausea and fever (Supplementary Figures S5-11). Compared to MISO, MIFE+MISO was associated with a lower risk ratio for developing fever (RR 0.33, 95% CI 0.19-0.57), nausea (RR 0.42, 95% CI 0.24-0.72) and vomiting (RR 0.55, 95% CI 0.32-0.94). Fewer women needed analgesia post treatment in the EVAC group compared to MISO (RR 0.43, 95% CI 0.27-0.68). Those who opted for EXP also used more analgesia compared to EVAC (RR 2.07, 95% CI 1.25-3.41) (Supplementary Figure S12). Women's satisfaction was similar for all the treatment options (Supplementary Figure S13). Supplementary Table SIII provides a summary of effect estimates for all secondary outcomes across treatment options.

Table II summaries the calculated SUCRA and mean rank for the secondary outcomes by the treatment options. Generally, MIFE+MISO had high ranking (low likelihood) for causing common gastrointestinal (GI) side effects (nausea (SUCRA 93.1%), vomiting (SUCRA 84%) and diarrhoea (SUCRA 63.2%)) and fever (SUCRA 86.8%). MVA had higher ranking (low likelihood) for post-treatment infection (SUCRA 87.6%) and serious complications (SUCRA 79.2%) with the highest likelihood for post-treatment satisfaction (SUCRA 98%). Women opting for EVAC had higher likelihood of requiring post-treatment blood transfusion (SUCRA 14.7%).

Discussion

Main findings

Our comprehensive meta-analysis showed that for managing first-trimester miscarriage, EXP had lower effectiveness to achieve complete evacuation of products of conception compared to other treatment options. Overall, there was similar effectiveness for the medical (MIFE+MISO and MISO) and the surgical options (MVA, D+C, and EVAC), with similar safety profiles reported. There was limited evidence to support the use of MISO+EVAC with no information on its safety profile. Evidence on the use of MIFE+MISO suffered from significant inconsistency. Overall, the addition of MIFE to MISO seems to improve its effectiveness with reduced likelihood of side effects but more research is needed to address the perceived inconsistency between direct and indirect evidence. Women's satisfaction was similar for all the options compared.

Currently, EXP is recommended as the first-line treatment option for first-trimester miscarriage (The National Institute for Health and Care Excellence, 2012). Women opting for this approach should be counselled objectively about the chances of needing further treatment, potential complications such as requiring blood transfusion (SUCRA 36.3%) or more analgesia (SUCRA 37.4%), and the availability of other effective treatment options. Excessive bleeding and repeated blood transfusion contribute to prolonged hospital stays and long-term adverse outcomes such as alloimmunisation (Royal College of Obstetricians and Gynaecologists, 2015) which are infrequently assessed in randomised trials.

Strength and limitations

This review, to our knowledge, is the first to provide a comprehensive evidence synthesis with network meta-analysis on all current treatment options for first-trimester miscarriage.

We conducted a systematic review of the literature with no search limitations. We assessed and found little evidence of small study effect with the funnel plot analysis raising confidence in our findings. We assessed the risk of bias using the Cochrane risk of bias assessment tool (Higgins *et al.*, 2011) which demonstrated low to moderate risk of bias in the majority of included studies. Compared to previously conducted meta-analysis (Nanda *et al.*, 2006; Neilson *et al.*, 2006, 2013; Sotiriadis *et al.*, 2005; Wen *et al.*, 2008), our study provides higher confidence supporting the role of medical treatment options for first trimester miscarriage, incorporating indirect evidence and ranking treatments likelihood for effectiveness and side effects.

Our findings are not without limitations. We were unable to accommodate for potential effect modifiers such as variation in population characteristics relevant to age, parity, size of products of conception, presence of side effects before randomisation and treatment settings. A large gestation sac might require a higher doses of MISO to achieve complete evacuation (Neilson *et al.*, 2006). Evidence on some treatment options, such as MVA, was sought primarily from low/middle income countries, which could suggest variations in local practice and geographical bias to one treatment option over the others.

There were variations in the ultrasound criteria used to diagnose the type of miscarriage (missed vs incomplete) and the primary outcome of complete evacuation of products of conception. The use of a standardised ultrasound criteria for the diagnosis of miscarriage is only recent and some of the included trials pre-date the currently established guidelines (The National Institute for Health and Care Excellence, 2012). To be pragmatic, we opted to keep those trials and offer a comprehensive and accurate review of the available literature. Similarly, there was variation in the type of included miscarriages (missed vs incomplete) in

each trial with some trials randomising either or both or simply not reporting on it (Table 1). Due to the risk of inconsistency, we were unable to generate evidence on the management of each type of miscarriage and our findings remain pragmatic. Such variation could be best addressed using an individual participant data meta-analysis.

There was inconsistency within the network (Supplementary Table SI) specifically within evidence loops comparing MIFE+MISO to other treatment options. We were unable to attribute this inconsistency to a particular effect modifier and adjusted for it using established models. Inconsistency could be attributed to the variations in the dosages and the routes of administration of MISO among included trials. Typically, MISO is used in sequential doses of 200 mcg and stopped once complete evacuation of products is achieved; this could present inherent inconsistency among trials. Quality evidence on the most effective dose with the least side effect is yet to emerge (Neilson *et al.*, 2006).

Variations in defining endpoints and the follow-up period limited the information on important long term outcomes such as uterine adhesions, pre-term birth and future fertility. Recent evidence suggest an increased risk for pre-term birth with multiple dilation and curettage (Lemmers *et al.*, 2015). Future work should focus on following up randomised cohorts to capture such outcomes.

To be pragmatic, evidence on MISO+EVAC, sought from one trial (Fang *et al.*, 2009), was kept within our network in view of its wide use in current practice. The findings of this trial should be interpreted with caution due to its small sample size, moderate risk of bias and limited reporting on secondary outcomes. We planned to report on four additional outcomes

in our protocol (hospital stay, changes in haemoglobin, anxiety, and depression). This, however, was not possible due to the large variability in reported end points.

We judged blinding to be possible in seven studies (Bagratee *et al.*, 2004; Blohm *et al.*, 2005; Herabutya and O-Prasertsawat, 1997; Lister *et al.*, 2005; Ngai *et al.*, 2001; Nielsen *et al.*, 1999; Wood and Brain, 2002). Of these, only four (Bagratee *et al.*, 2004; Blohm *et al.*, 2005; Lister *et al.*, 2005; Sinha *et al.*, 2018) were blinded, introducing a potential risk of bias. Lack on information on blinding for outcomes assessment is another limitation in the included studies.

Interpretation of findings

Our study supports the use of medical treatments as a potential substitute for surgery, however, studies to establish the lowest effective dose of MISO are needed (Neilson *et al.*, 2006). A higher dose of MISO is likely to cause more side effects such as nausea and vomiting (Tang *et al.*, 2007). Medical management could be considered as a cost-effective first-line treatment option. The woman's preference is an important factor to consider when offering the various treatment options, often influenced by their carer's advice. There was seldom consideration in the included studies for reporting outcomes important to the women undergoing miscarriage, such as post-treatment anxiety and depression. None of the included studies reported on the tolerability of each treatment option which can aid women to identify their preferred choice. Developing a core outcome set with input from all stakeholders should be considered in future research (Khan, 2016).

Recently, MIFE has been more commonly combined with MISO to improve the effectiveness of medical treatment for uterine evacuation (Spitz *et al.*, 1998). Our analysis, seeking direct and mixed evidence, suggests some added value compared to using MISO alone for first-

trimester miscarriage but with limited confidence due to the perceived inconsistency among included trials. Considering its high cost, a cost-effectiveness evaluation is needed to establish the value of using MIFE+MISO routinely. Using MISO for priming the cervix before EVAC has been suggested to reduce the need for dilation and trauma to the endometrium (Lawrie *et al.*, 1996). Evidence to support the effectiveness and safety of this practice for managing first trimester miscarriage is scarce (only one randomised trial of 75 women) (Fang *et al.*, 2009) and more trials are needed to justify the potentially increased cost and side effects.

Outpatient use of MVA with direct access to operating theatres could offer cost reduction (Magotti *et al.*, 1995). While EXP is arguably cheaper than other treatment options, the higher probability of complications might increase its associated cost. There is a need for a comprehensive economic evaluation with extended decision models to accommodate for the effectiveness of all available treatment options and potential adverse outcomes (Strand, 2015). Comprehensive policymaking including all available treatment options could offer better value for money and facilitate higher patient satisfaction (Dalton *et al.*, 2015; Molnar *et al.*, 2000; Wallace *et al.*, 2010) (Supplementary Figure S2).

Our study provides important insight for various stakeholders involved in caring for women with first trimester miscarriage. Future work should aim to involve stakeholders' views prospectively on relevant health outcomes to provide safe and cost-effective care. Efforts to standardise treatment options and reduce selective reporting of outcomes are warranted to reduce inconsistency in evidence synthesis.

Conclusions

Medical treatments for first-trimester miscarriage have similar effectiveness and side effects compared to surgery. The addition of MIFE could increase the effectiveness of MISO and reduce side effects though evidence is limited due to inconsistency. EXP has lower effectiveness compared to other treatment options.

Acknowledgements:

The authors acknowledge the initial contribution of Arri Coomarasamy, Ioannis Gallos and Mary Eyo.

Authors' roles:

BHA conceived the idea, performed the search, extracted data and wrote the first draft. NM extracted data; AT and JZ performed the analysis and revised the manuscript; KSK revised the manuscript and supervised the study. All authors provided critical input to the final manuscript.

Funding:

No funding was received in support of this work.

Conflict of interest:

None

Figures and tables legends:

Figure 1: The study selection process for network meta-analysis on management of first trimester miscarriage.

Figure 2: Network of treatment options for first trimester miscarriage. Options: expectant management (EXP), sharp dilation and curettage (D+C), electric vacuum aspiration (EVAC), manual vacuum aspiration (MVA), misoprostol alone (MISO), mifepristone+misoprostol (MIFE+MISO) or misoprostol+electric vacuum aspiration (MISO+EVAC).
The size of the dots represents the number of women randomised to each treatment option and the thickness of the lines represents the number of randomised trials with head to head comparison between each two treatment options.

Figure 3: Direct (D) and mixed (M) evidence meta-analysis for treatment options for first trimester miscarriage. Options: expectant management (EXP), sharp dilation and curettage (D+C), electric vacuum aspiration (EVAC), manual vacuum aspiration (MVA), misoprostol alone (MISO), mifepristone+misoprostol (MIFE+MISO) or misoprostol+electric vacuum aspiration (MISO+EVAC).

Figure (4): The mean rank and cumulative rank probability (SUCRA) of effectiveness for each treatment option for first trimester miscarriage. Options: expectant management (EXP), sharp dilation and curettage (D+C), electric vacuum aspiration (EVAC), manual vacuum aspiration (MVA), misoprostol alone (MISO), mifepristone+misoprostol (MIFE+MISO) or misoprostol+electric vacuum aspiration (MISO+EVAC).

Treatments with the top mean rank and the largest area under the curve have the highest probability of achieving the primary outcome of complete evacuation of products of conception.

Table I: Characteristics of included trials evaluating treatment options for first trimester miscarriage.

Table II: Summary of the calculated mean rank and the surface under the cumulative ranking curve (SUCRA) for the secondary outcomes for the treatment options for first trimester miscarriage.

Treatments ranked first have lower likelihood to achieving adverse outcomes and higher likelihood of post-treatment satisfaction. Treatments with a higher SUCRA score have lower likelihood of achieving adverse outcomes and higher likelihood of post-treatment satisfaction.

Supplementary Figure S1: Risk of bias in included trials on the treatment options for first trimester miscarriage.

Supplementary Figure S2: Flow chart for the management of women with first trimester miscarriage.

Supplementary Figure S3: Mixed evidence meta-analysis adjusted for inconsistency for treatment options for first trimester miscarriage.

Supplementary Figure S4: Funnel plot of the treatment effect for included trials on treatment options for first trimester miscarriage.

Supplementary Figure S5: Mixed evidence network meta-analysis of blood transfusion following treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C) SUCRA.

Supplementary Figure S6: Mixed evidence network meta-analysis of infection/pelvic inflammatory disease following treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C) SUCRA.

Supplementary Figure S7: Mixed evidence network meta-analysis of serious complications following treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C) SUCRA.

Supplementary Figure S8: Mixed evidence network meta-analysis of diarrhoea following treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C) SUCRA.

Supplementary Figure S9: Mixed evidence network meta-analysis of vomiting following treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C) SUCRA.

Supplementary Figure S10: Mixed evidence network meta-analysis of nausea following treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C) SUCRA.

Supplementary Figure 11: Mixed evidence network meta-analysis of fever following treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C) SUCRA.

Supplementary Figure 12: Mixed evidence network meta-analysis of analgesia following treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C) SUCRA.

Supplementary Figure 13: Mixed evidence network meta-analysis of women's satisfaction following treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C) SUCRA.

Supplementary Table SI: Side-split analysis of inconsistency in the network of treatment options for first trimester miscarriage.

Supplementary Table SII: Summary of risk of bias for included studies.

Supplementary Table SIII: League table of effect estimates for secondary outcomes across treatment options for first trimester miscarriage.

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