

A systematic review of the effectiveness, safety, and acceptability of medical management of intrauterine fetal death at 14–28 weeks of gestation

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Abstract

Background: Optimal dose, interval, and administration route of misoprostol with added benefit of mifepristone for management of second trimester intrauterine fetal death (IUFD) are not established.

Objectives: To assess effectiveness, safety, and acceptability of medical management of second trimester IUFD.

Search strategy: Research databases from January 2006 to October 2018.

Selection criteria: Randomized controlled trials with IUFD cases at 14–28 weeks of gestation.

Data collection and analysis: We screened and extracted data, assessed risk of bias, conducted analyses, and assessed overall certainty of the evidence.

Main results: Sixteen trials from 1695 citations. When misoprostol is used alone, 400 µg is more effective than 200 µg (RR 0.78; 95% CI, 0.66–0.92, moderate certainty evidence); the sublingual route is more effective than the oral route (RR 0.88; 95% CI, 0.70–1.11, low certainty evidence). There may be little to no difference between the sublingual and vaginal route (RR 0.93; 95% CI, 0.85–1.03, low certainty evidence). Certainty of evidence related to mifepristone–misoprostol regimens and safety and acceptability is very low.

Conclusions: Misoprostol 400 µg every 4 hours, sublingually or vaginally, may be effective. We cannot draw conclusions about safety and acceptability, or about the added benefits of mifepristone.

KEYWORDS

Intrauterine fetal death; Medical management; Mifepristone; Misoprostol; Second trimester; Systematic review

1 | INTRODUCTION

While rare, second trimester intrauterine fetal death (IUFD) can be a psychologically stressful event. Approximately 1% of all pregnancies are complicated by IUFD¹; however, the exact incidence in the second

trimester is unknown. Factors contributing to IUFD include fetal malformations and chromosomal abnormalities, uterine complications, umbilical cord pathology, maternal medical conditions, and infection,^{2,3} although etiology is often unexplained.² In the event of a fetal death, most women will start contracting spontaneously within 3 weeks.

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Active rather than expectant management is often favored because of the increased risk to the mother, secondary to retained products of conception.¹ Additional concerns for the woman include the risk of uterine rupture and disseminated intravascular coagulation.¹

Medical management is considered a safe and effective treatment option for IUFD.⁴ One common medication used to treat IUFD is misoprostol,¹ which is a synthetic prostaglandin E1 analogue. Misoprostol is effective in emptying the uterus owing to its ability to induce uterine contractions and soften the cervix.⁴ Adverse effects are often mild and include nausea, vomiting, diarrhea, fever, chills, bleeding, and pain due to uterine contractions.⁴ Several misoprostol regimens exist, including use alone or with other agents such as mifepristone. Studies evaluating the safety, effectiveness, and acceptability of the drug alone and/or in combination with mifepristone have often included viable pregnancies with induced abortion or labor induction.⁵ Previous systematic reviews including IUFD have not focused exclusively on the second trimester or consistently defined IUFD; as such, limited guidance has been provided for pregnancies at 14–28 weeks of gestation.^{6–8}

Questions pertaining to the optimal dose, interval, and route of administration of misoprostol, as well as the added benefit of mifepristone for management of second trimester IUFD still remain. The aim of the present systematic review is to address these knowledge gaps by assessing the effectiveness, safety, and acceptability of medical management of second trimester IUFD. This review was conducted as part of the evidence base for World Health Organization (WHO) recommendations on medical management of abortion.

2 | MATERIALS AND METHODS

At the outset of this review, the most recent systematic review focusing on medical management of IUFD included randomized controlled trials and was conducted in 2006.⁸ We sought to update this review focusing on medical management using mifepristone and/or misoprostol for pregnancies at 14–28 weeks of gestation.

We conducted searches in PubMed, Embase, Global Index Medicus, Popline, and the Cochrane Central Register of Controlled Trials (CENTRAL) on March 7, 2017, and the search was rerun on October 4, 2018. The search strategy (supplementary information Appendix S1) was developed together with experts working in systematic review literature searching at WHO, Geneva, and Karolinska Institutet, Stockholm. Our search strategy was formed by combining two concepts: (1) IUFD; and (2) misoprostol. The key words used were “fetal death”; “abortion, missed”; and “misoprostol” to capture studies using various terms to describe IUFD, and those that used misoprostol alone and a combination of mifepristone and misoprostol (combined regimen). MeSH terms were used when applicable. The search strategy was customized to each electronic database with no language restrictions.

We hand searched the reference lists from three systematic reviews that included second trimester IUFD,^{6–8} and the reference lists

of eligible trials identified through our search. There was no patient or public involvement in the development of this review.

We included randomized controlled trials with cases of IUFD at between 14 and 28 weeks of gestation, where cases were evenly distributed between study arms. Trials including IUFD below 14 weeks or above 28 weeks of gestation were only considered if the mean gestational age of the participants was within 14–28 weeks. Trials were selected for inclusion if they included comparisons of misoprostol alone or a combined regimen using different routes or dosages of misoprostol. Trials comparing misoprostol alone or a combined regimen with expectant care, placebo, or surgery were also included.

Two reviewers conducted the screening, data extraction, and assessment of risk of bias, in parallel. Standardized screening and data extraction forms were created prior to data collection. Titles and abstracts were screened, and full text was obtained if both reviewers judged a citation to be potentially eligible. Risk of bias was assessed in included studies in accordance with the Cochrane Handbook.⁹ Selection, performance, detection, attrition, and reporting bias were considered key domains in the summary assessment of risk of bias within each trial (Table S1).¹⁰ Any discrepancies were reviewed and discussed between the authors and resolved together.

We included trials where the primary effectiveness outcome was complete abortion, defined in this review as complete expulsion of products of conception, measured within 24 or 48 hours (utilizing a variety of assessment methods, including ultrasound or clinical signs and symptoms). Other effectiveness outcomes were induction to expulsion interval (time from treatment initiation to complete abortion) and need for surgical intervention. Our safety outcome was measured as number of serious adverse events (SAEs; such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete removal of products, or death). Secondary outcomes included adverse effects (including nausea, vomiting, fever, pain, and hemorrhage) and acceptability (measured in satisfaction). A core outcome set related to abortion exists (<http://www.crown-initiative.org/core-outcome-sets/ongoing-core-outcome-sets/>); however, since it is still in development it has not been used in this review.

We used RevMan as our analysis tool.¹¹ For dichotomous outcomes we analyzed data based on number of events and number of women assessed in the intervention and comparison groups. We used these to calculate the relative risk (RR) and 95% confidence interval (CI). For continuous outcomes we reported the measure as mean \pm SD. We used an online converter (http://vassarstats.net/median_range.html) and the recalculation method proposed by the Cochrane Training group (<http://training.cochrane.org/resource/analyzing-continuous-outcomes>). The certainty of the evidence using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias)¹² were assessed and presented alongside the findings in the tables.

As the present systematic review is based on existing published literature, no ethical clearance was required.

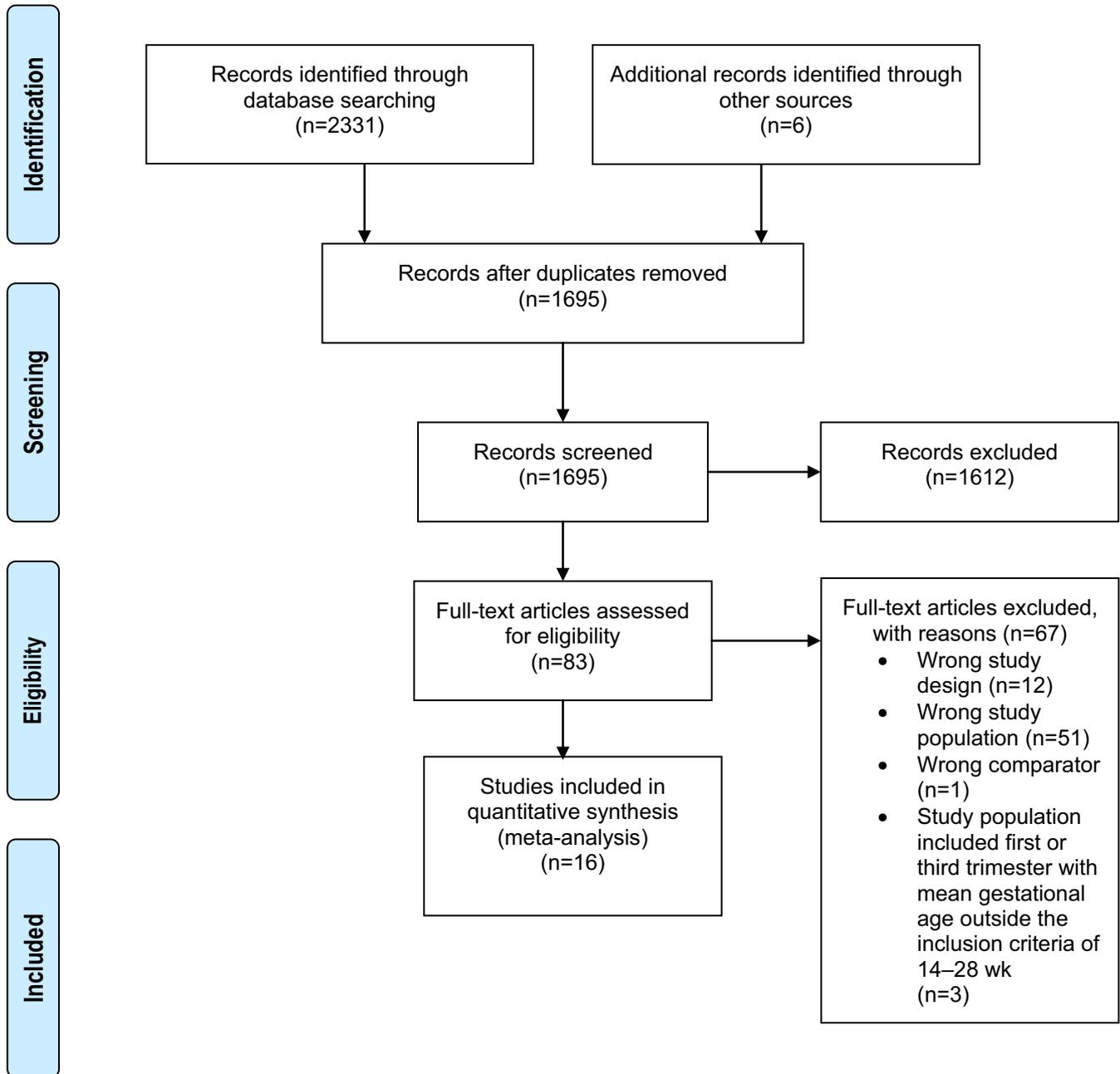


FIGURE 1 Flow diagram of included and excluded studies.

3 | RESULTS

The initial search generated 1695 citations after duplicates were removed. Eighty-three full texts were screened, of which 67 were excluded. Six additional trials^{13–18} identified from three systematic reviews^{6–8} were included. We contacted the authors of included trials where additional information was needed. We received information from four trial authors,^{19–22} with two providing disaggregated IUFD data.^{19,20} The flow of included and excluded trials is presented in Figure 1.

The characteristics of the included trials are presented in Table 1. We included 16 trials with a total of 1890 participants. Four

trials^{14,15,19,23} included women with a single prior uterine incision; one trial²¹ stated that women with a prior uterine incision were eligible but it is unclear how many were included. No direct evidence related to medical management compared with surgical, expectant, or placebo management was identified. Four trials reported that the analysis was intention-to-treat (ITT) analysis.^{18,20,23,24} Thus, it was not possible to perform true ITT analyses for all comparisons and outcomes.

One trial compared mifepristone and misoprostol versus misoprostol alone.²⁰ Misoprostol was administered vaginally every 6 hours. Women treated with the combined regimen had slightly higher rates of complete abortion within 24 hours (RR 1.18; 95% CI, 0.91–1.53) and

TABLE 1 Study characteristics of the 16 included studies.

Author, y	Methods	Participants	Intervention	Risk of bias
Bracken et al. 2014 ²⁴	Simple randomization sequence generated by computer with blocks of 10 and stratified by study site	Women with IUFD. Gestational age 14–28 wk	Misoprostol 200 µg vs 100 µg misoprostol buccally 6-hourly, max 8 doses	Low
Brouns et al. 2010 ²³	Computer-generated randomization	Women with IUFD, congenital malformations, psychosocial reasons. Gestational age 14–24 wk	Mifepristone 200 mg followed by 200 µg misoprostol vs 400 µg misoprostol vaginally 4-hourly	Low
Calliskan et al. 2005 ¹⁵	Computer stratified and restricted randomization generated in a secure website	Women with IUFD, early rupture of membranes, fetal anomaly, exposure to teratogens, severe maternal medical problems, and congenital infections. Gestational age 13–20 wk	100 µg oral misoprostol 2-hourly vs 200 µg vaginal misoprostol 4-hourly vs 100 µg sublingual misoprostol 2-hourly	Low or unclear
Calliskan et al. 2009 ¹⁹	Nonrestricted, computer-generated randomization	Women with IUFD. Gestational age 15–22 wk	100 µg sublingual misoprostol vs 200 µg sublingual misoprostol every 2 h, max 12 doses	Low
Chaudhuri et al. 2015 ²⁰	A computer analyst, not involved with the trial, generated the random number sequence	Women with IUFD. Gestational age 20–28 wk	Mifepristone or placebo followed by 100 µg vaginal misoprostol 6-hourly, max 4 doses (≥26 wk: 50 µg, max 6 doses)	Low
Chittacharoen et al. 2003 ¹⁶	Computer-generated random numbers randomization in sealed opaque envelopes	Women with IUFD. Gestational age 16–41 wk	400 µg oral misoprostol 4-hourly vs 200 µg vaginal misoprostol 12-hourly	Low or unclear
Dickinson et al. 2002 ¹⁴	Random number tables	Women with IUFD, fetal anomaly, maternal reasons. Gestational age 14–30 wk	200 µg vaginal misoprostol 6-hourly vs 400 µg vaginal misoprostol 6-hourly vs a loading dose of 600 µg misoprostol followed in 6 h by 200 µg vaginal misoprostol 6-hourly, max 48 h	Low or unclear
Elhassan et al. 2008 ²⁵	Method of generating the randomization sequence not specified	Women with IUFD. Gestational age 13–28 wk	100 µg sublingual misoprostol 4-hourly vs 100 µg vaginal misoprostol 4-hourly vs 100 µg oral misoprostol 4-hourly. Repeated once if unsuccessful after 24 h	Low or unclear
Eslamian et al. 2007 ²¹	Computer-generated random number table	Women with IUFD, premature rupture of membranes, maternal medical disorders, lethal fetal congenital malformation. Gestational age 14–24 wk	400 µg vaginal misoprostol 6-hourly vs 200 µg vaginal misoprostol 6-hourly, max 6 doses	Low or unclear
Fadalla et al. 2004 ¹⁷	Method of generating the randomization sequence not specified	Women with IUFD. Gestational age 13–28 wk	100 µg oral misoprostol 4-hourly vs 100 µg vaginal misoprostol 4-hourly	Low or unclear
Feldman et al. 2003 ¹⁸	Computer-generated random numbers	Women with IUFD, fetal abnormality, preterm premature rupture of membranes. Gestational age 14–23 wk	800 µg vaginal misoprostol followed by 400 µg oral misoprostol 8-hourly vs 800 µg vaginal misoprostol followed by 400 µg vaginal misoprostol 8-hourly	Low or unclear
Kurshid et al. 2010 ²⁶	Method of generating the randomization sequence not specified	Women with IUFD, fetal abnormality, premature preterm rupture of membranes. Gestational age 19–23 wk	Misoprostol vaginally 800 µg followed by 400 µg oral misoprostol vs 400 µg vaginal misoprostol 8-hourly	Low or unclear
Niromanesh et al. 2005 ¹³	Method of generating the randomization sequence not specified	Women with IUFD. Gestational age 14–25 wk	400 µg vaginal misoprostol 12-hourly vs 600 µg vaginal misoprostol, max 48-hourly	Low or unclear

(Continues)

TABLE 1 (Continued)

Author, y	Methods	Participants	Intervention	Risk of bias
Rahimi-Sharbat et al., 2015 ²⁷	A computer-generated randomization sequence, blocks of six	Women with IUFD, fetal anomaly, premature rupture of membranes, oligohydramnios, other (not specified), aneuploidy. Gestational age 13–24 wk	400 µg vaginal misoprostol vs 400 µg sublingual misoprostol vs 400 µg vaginal misoprostol followed by 400 µg sublingual misoprostol 4-hourly up to 48 hours, max 5 doses within 24 h	High risk of bias for one or more key domains
Usmani et al., 2013 ²²	Method of generating the randomization sequence not specified	Women with IUFD, fetal anomaly, premature rupture of membranes. Gestational age 13–26 wk	400 µg oral misoprostol 4-hourly vs 400 µg vaginal misoprostol 4-hourly, max 5 doses	High risk of bias for one or more key domains
Yilmaz et al., 2007 ²⁸	Computer-generated randomization	Women with IUFD, fetal anomaly, chromosomal anomaly, others (not specified). Gestational age 14–24 wk	Saline moistened 800 µg vaginal misoprostol 6-hourly vs dry misoprostol 800 µg vaginally 6-hourly, max 3 doses in 24 h	Low

a shorter expulsion time than women treated with misoprostol alone. No SAEs were reported among 27 participants. The evidence is very low for all reported outcomes (Table 2A). The effect estimates for all the outcomes were based on ITT analysis.

One trial compared different dosages of misoprostol when combined with mifepristone.²³ Misoprostol was administered vaginally every 4 hours. Women treated with 200 µg misoprostol compared with 400 µg had lower rates of complete abortion within 24 hours (RR 0.90; 95% CI, 0.74–1.10) with little to no difference in expulsion time (low certainty evidence). Seven SAEs were reported in total among 176 participants: three of 90 women in the 400-µg group and four of 86 women in the 200-µg group required a blood transfusion (Table 2B). Women in the 200-µg group had lower rates of adverse effects (supplementary information Table S1). The effect estimates for all the outcomes were based on ITT analysis.

Five trials compared different dosages of misoprostol and included comparisons of 100 µg versus 200 µg,^{19,24} 200 µg versus 400 µg,^{14,21} and 400 µg versus 600 µg¹³ (Table 3).

Two trials compared 100 µg misoprostol with 200 µg misoprostol.^{19,24} In these trials misoprostol was administered sublingually and buccally every 2 and 6 hours, respectively. Women treated with 100 µg had lower rates of complete abortion within 48 hours (RR 0.90; 95% CI, 0.74–1.0, low certainty evidence). No surgical events were reported and one SAE (continued hospitalization owing to failed expulsion) was reported in the 200-µg group (Table 3A). Fewer women in the 100-µg group reported diarrhea and there was little to no difference in reported pain compared with the 200-µg group (low certainty evidence). Fewer women in the 100-µg group were satisfied (low certainty evidence) (supplementary information Table S2A).

Two trials compared 200 µg of misoprostol with 400 µg misoprostol.^{14,21} In these trials misoprostol was administered vaginally every 6 hours. There was moderate certainty evidence that the 200-µg dose was less effective when considering complete abortion (24 hours: RR 0.79; 95% CI, 0.39–1.63; 48 hours: RR 0.79; 95% CI, 0.64–0.98) and expulsion time. The trials did not report on SAEs (Table 3B). Women treated with the lower dose reported more pain and diarrhea (low certainty evidence), but less vomiting (moderate certainty evidence) (supplementary information Table S2B).

One trial compared two doses of misoprostol, 600 µg versus 400 µg, administered vaginally every 12 hours.¹³ The 600 µg dose was slightly more effective in terms of completeness within 24 hours (RR 0.90; 95% CI, 0.8–1.0) but within 48 hours there may be little to no difference (RR 0.98; 95% CI, 0.93–1.04). The 600-µg dose resulted in shorter expulsion time (low certainty evidence). The trial did not report on SAEs (Table 3C). Rates of pain and diarrhea were lower among women treated with 400 µg, but rates of vomiting were similar between groups. The certainty of evidence is very low for all reported adverse effects (supplementary information Table S2C).

One trial compared regimens with and without a loading dose.¹⁴ Repeat doses of misoprostol were administered vaginally every 6 hours. A loading dose of 600 µg misoprostol followed by 200 µg misoprostol, compared with repeat doses of 200 µg alone, resulted in higher rates of complete abortion (24 hours: RR 0.74; 95% CI,

TABLE 2 Comparison of different mifepristone–misoprostol regimens.

Outcome	Comparison	Intervention	RR (95% CI) ^a	No. people (no. studies)	GRADE	Plain language conclusion
(A) Mifepristone followed by misoprostol (intervention) vs misoprostol alone (comparison): Chaudhuri 2015 ²⁰ (separate data for IUFD n=27)						
Complete abortion (24 h)	85 per 100	100 per 100 (77 to 100)	RR 1.18 (0.91–1.53)	27 (1 RCT)	⊕○○○ Very low ^b	We are uncertain of the effect—the certainty of the evidence is very low
Complete abortion (48 h)						No direct evidence identified
Induction to expulsion (h)		The mean interval was 6.3 h shorter (–9.25 to –3.35)		27 (1 RCT)	⊕○○○ Very low ^b	We are uncertain of the effect—the certainty of the evidence is very low
Surgical intervention	0 per 13	0 per 14		27 (1 RCT)		We are uncertain of the effect—the effect estimate could not be estimated
Safety (SAEs)	0 per 13	0 per 14		27 (1 RCT)		We are uncertain of the effect—the effect estimate could not be estimated
(B) Mifepristone followed by 200 µg misoprostol (intervention) vs mifepristone followed by 400 µg misoprostol (comparison): Brouns 2010 ²³ (n=176)						
Complete abortion (24 h)	73 per 100	66 per 100 (54 to 81)	RR 0.90 (0.74–1.10)	176 (1 RCT)	⊕⊕○○ Low ^c	In the intervention group there may be fewer women with complete abortion within 24 h ^a
Complete abortion (48 h)						No direct evidence identified
Induction to expulsion (h)	The median interval was 9.9 h (range 8.7–11.2)	The median interval was 9.3 h (range 7.7–10.8)		176 (1 RCT)	⊕⊕○○ Low ^c	There may be little or no change in the induction to expulsion interval
Surgical intervention	8 per 100	8 per 100 (3 to 22)	RR 1.05 (0.38–2.86)	176 (1 RCT)	⊕○○○ Very low ^b	We are uncertain of the effect—the certainty of the evidence is very low
Safety (SAEs)	3 per 100	5 per 100 (1 to 20)	RR 1.40 (0.32–6.05)	176 (1 RCT)	⊕○○○ Very low ^b	We are uncertain of the effect—the certainty of the evidence is very low

Abbreviations: CI, confidence interval; RR: relative risk; SAEs, serious adverse events.

^aThe confidence interval (95% CI) around the effect estimate indicates both a positive and negative effect.

^bGRADE explanation: Downgraded three levels in certainty due to very serious imprecision.

^cGRADE explanation: Downgraded two levels in certainty due to serious imprecision.

0.56–0.97; 48 hours: RR 0.82; 95% CI, 0.65–1.03, low certainty evidence) and shorter expulsion time. The number of surgical interventions was higher in the group that received a loading dose (low certainty evidence). The trial did not report on SAEs (Table 4A). Women who received a loading dose experienced more vomiting and pain, but less diarrhea. The certainty evidence is very low for all reported adverse effect outcomes (supplementary information Table S3A).

The same trial¹⁴ compared a loading dose followed by 200 µg with repeat doses of 400 µg alone. There may be little to no difference in complete abortion rates (24 hours: RR 0.95; 95% CI, 0.77–1.18; 48 hours: RR 0.93; 95% CI, 0.76–1.14, low certainty evidence) between the two regimens. There was low certainty evidence that

women who received a loading dose had slightly shorter expulsion time (Table 4B). Women who did not receive a loading dose experienced less pain and diarrhea and reported similar frequency of vomiting. The certainty of evidence for all reported adverse effects is very low (supplementary information Table S3B).

Seven trials compared various routes of misoprostol including oral versus sublingual route,^{15,25} oral versus vaginal route,^{17,18,22,25,26} and vaginal versus sublingual route^{25,27} (Table 5).

Two trials compared the sublingual route with the oral route.^{15,25} In these trials a dose of 100 µg misoprostol was administered every 2 and 4 hours, respectively. The sublingual route was more effective when considering completeness (RR 0.88; 95% CI, 0.70–1.11) and

TABLE 3 Comparison of different dosages of misoprostol when misoprostol is used alone.

Outcome	Comparison	Intervention	RR (95% CI)	No. people (no. studies)	GRADE	Plain language conclusion
(A) 100 µg misoprostol (intervention) vs 200 µg misoprostol (comparison); Bracken 2014, ²⁴ Caliskan 2009 ¹⁹ (separate data for IUFD n=56)						
Complete abortion (24 h)	79 per 100	62 per 100 (31 to 100)	RR 0.79 (0.39–1.63)	204 (2 RCTs)	⊕○○○ Very low ^{a,b}	We are uncertain of the effect—the certainty of the evidence is very low
Complete abortion (48 h)	78 per 100	62 per 100 (50 to 76)	RR 0.79 (0.64–0.98)	153 (1 RCT)	⊕⊕○○ Low ^b	In the intervention group there may be fewer women with complete abortion within 48 h
Induction to expulsion (h)		The mean interval was 1.66 h longer (–4.89 shorter to +8.21)		158 (2 RCTs)	⊕○○○ Very low ^{a,b}	We are uncertain of the effect—the certainty of the evidence is very low
Surgical intervention	0 per 26	0 per 25		51 (1 RCT)		We are uncertain of the effect—the effect estimate could not be estimated
Safety (SAEs)	1 per 103	0 per 101		204 (2 RCTs)		We are uncertain of the effect—the effect estimate could not be estimated
(B) 200 µg misoprostol (intervention) vs 400 µg misoprostol (comparison); Dickinson 2002, ¹⁴ Eslamian 2007 ²¹						
Complete abortion (24 h)	78 per 100	61 per 100 (51 to 72)	RR 0.78 (0.66–0.92)	263 (2 RCTs)	⊕⊕⊕○ Moderate ^c	In the intervention group there are probably fewer women with complete abortion within 24 h
Complete abortion (48 h)	89 per 100	81 per 100 (75 to 88)	RR 0.91 (0.84–0.98)	263 (2 RCTs)	⊕⊕⊕○ Moderate ^c	In the intervention group there are probably fewer women with complete abortion within 48 h
Induction to expulsion (h)		The mean interval was 5.31 h longer (4.0 to 6.62)	–	263 (2 RCTs)	⊕⊕⊕○ Moderate ^c	Women in the intervention group probably have a longer mean induction to expulsion interval
Surgical intervention	71 per 100	54 per 100 (30 to 98)	RR 0.76 (0.42–1.38)	263 (2 RCTs)	⊕○○○ Very low ^{a,b}	We are uncertain of the effect—the certainty of the evidence is very low
Safety (SAEs)						No direct evidence identified
(C) 400 µg misoprostol (intervention) vs 600 µg misoprostol (comparison); Niromanesh 2005 ¹³						
Complete abortion (24 h)	98 per 100	88 per 100 (78 to 98)	RR 0.90 (0.8–1.0)	100 (1 RCT)	⊕⊕○○ Low ^{c,d}	In the intervention group there may be fewer women with complete abortion within 24 h
Complete abortion (48 h)	100 per 100	98 per 100 (93 to 100)	RR 0.98 (0.93–1.04)	100 (1 RCT)	⊕⊕○○ Low ^{c,d}	There may be little or no change in the number of women with complete abortion within 48 h
Induction to expulsion (h)		The mean interval was 3 h longer (0.17 to 5.83)	–	100 (1 RCT)	⊕⊕○○ Low ^{c,d}	Women in the intervention group may have a longer mean induction to expulsion interval
Surgical intervention	20 per 100	14 per 100 (6 to 34)	RR 0.70 (0.29–1.69)	100 (1 RCT)	⊕○○○ Very low ^{b,d}	We are uncertain of the effect—the certainty of the evidence is very low
Safety (SAEs)						No direct evidence identified

Abbreviations: CI, confidence interval; RR: relative risk; SAEs, serious adverse events.

^aGRADE explanation: Downgraded one level in certainty due to inconsistency.

^bGRADE explanation: Downgraded two levels in certainty due to serious imprecision.

^cGRADE explanation: Downgraded one level in certainty due to imprecision.

^dGRADE explanation: Downgraded one level in certainty due to unclear risk of bias.

TABLE 4 Comparison of loading doses vs no loading dose when misoprostol is used alone.

Outcome	Comparison	Intervention	RR (95% CI)	No. people (no. studies)	GRADE	Plain language conclusion
(A) 200 µg misoprostol (intervention) vs a loading dose of 600 µg misoprostol followed by 200 µg misoprostol (comparison): Dickinson 2002 ¹⁴						
Complete abortion (24 h)	80 per 100	60 per 100 (45 to 77)	RR 0.74 (0.56–0.97)	100 (1 RCT)	⊕⊕○○ Low ^a	In the intervention group there may be fewer women with complete abortion within 24 h
Complete abortion (48 h)	80 per 100	66 per 100 (52 to 82)	RR 0.82 (0.65–1.03)	100 (1 RCT)	⊕⊕○○ Low ^a	In the intervention group there may be fewer women with complete abortion within 48 h
Induction to expulsion (h)	Median interval was 13.2 h (IQR 11.2–21.7)	Median interval was 18.2 h (IQR 13.3–32.5)		100 (1 RCT)	⊕⊕○○ Low ^a	Women in the intervention group may have a longer mean induction to expulsion interval
Surgical intervention	41 per 100	24 per 100 (13 to 43)	RR 0.58 (0.32–1.05)	100 (1 RCT)	⊕⊕○○ Low ^a	In the intervention group there may be fewer women that need surgical intervention
Safety (SAEs)						No direct evidence identified
(B) 400 µg misoprostol (intervention) vs a loading dose of 600 µg followed by 200 µg misoprostol (comparison): Dickinson 2002 ¹⁴						
Complete abortion (24 h)	80 per 100	76 per 100 (61 to 94)	RR 0.95 (0.77–1.18)	99 (1 RCT)	⊕⊕○○ Low ^b	There may be little or no change in the number of women with complete abortion within 24 h ^a
Complete abortion (48 hrs)	82 per 100	76 per 100 (62 to 93)	RR 0.93 (0.76–1.14)	99 (1 RCT)	⊕⊕○○ Low ^b	There may be little or no change in the number of women with complete abortion within 24 h ^a
Induction to expulsion (h)	Median was 13.2 h (IQR 11.2–21.7)	Median was 15.1 h (IQR 10.9–23.7)		99 (1 RCT)	⊕⊕○○ Low ^b	Women in the intervention group may have a longer mean induction to expulsion interval
Surgical intervention	41 per 100	42 per 100 (26 to 67)	RR 1.03 (0.64–1.64)	99 (1 RCT)	⊕○○○ Very low ^c	We are uncertain of the effect—the certainty of the evidence is very low
Safety (SAEs)						No direct evidence identified

Abbreviations: CI, confidence interval; RR: relative risk; SAEs, serious adverse events.

^aThe confidence interval (95% CI) around the effect estimate indicates both a positive and negative effect.

^bGRADE explanation: Downgraded two levels in certainty due to serious imprecision.

^cGRADE explanation: Downgraded three levels in certainty due to very serious imprecision.

expulsion time (low certainty evidence). The trials did not report on SAEs (Table 5A). Regarding adverse effects, women using the oral route experienced more vomiting and diarrhea compared with the sublingual route group. The certainty of evidence was very low for all reported adverse effects (supplementary information Table S4A).

Five trials compared the vaginal route with the oral route.^{17,18,22,25,26} Three trials used a dose of 100 µg or 400 µg misoprostol every 4 hours^{17,22,25} and two trials used a loading dose of 800 µg misoprostol followed by 400 µg every 8 hours.^{18,26} The oral route was less effective when considering completeness (RR 0.78; 95% CI, 0.68–0.89, low certainty evidence). No SAEs were reported (Table 5B). Women using the oral route had higher rates of vomiting and diarrhea compared with the vaginal route, but pain rates were similar between the groups. The certainty of evidence was very low for all reported adverse effects (supplementary information Table S4B).

Two trials compared the sublingual route with the vaginal route.^{25,27} In these trials a dose of 100 µg and 400 µg misoprostol was administered

every 4 hours, respectively. There may be little to no difference in rates of complete abortion (24 hours: RR 0.93; 95% CI, 0.85–1.03; 48 hours: RR 0.98; 95% CI, 0.93–1.04, low certainty of evidence) between the two routes. Women who received misoprostol vaginally had longer expulsion times (low certainty evidence). The trials did not report on SAEs (Table 5C).

One trial compared different preparations of misoprostol.²⁸ A dose of 800 µg misoprostol was administered vaginally every 6 hours. Effectiveness of dry versus moist misoprostol was similar when considering rates of complete abortion (RR 1.00; 95% CI, 0.83–1.19, very low certainty evidence) and expulsion time (low certainty evidence). No SAEs were reported. Women using dry misoprostol had higher rates of surgical interventions (very low certainty evidence) (supplementary information Table S5).

Two trials compared misoprostol regimens using various dosages, routes, and intervals simultaneously^{15,16} (supplementary information Table S6). The findings from these trials, along with the certainty of evidence, are reported as supplementary information.

TABLE 5 Comparison of route of misoprostol when misoprostol is used alone.

Outcome	Comparison	Intervention	RR (95% CI)	No. people (no. studies)	GRADE	Plain language conclusion
(A) Oral misoprostol (intervention) vs sublingual misoprostol (comparison): Caliskan 2005¹⁵ and Elhassan 2008²⁵						
Complete abortion (24 h)	97 per 100	85 per 100 (68 to 100)	RR 0.88 (0.70–1.11)	202 (2 RCTs)	⊕⊕○○ Low ^{b,c}	In the intervention group there may be fewer women with complete abortion within 24 h ^a
Complete abortion (48 h)						No direct evidence identified
Induction to expulsion (h)		The mean interval was 7.5 h longer (0.56 to 13.75)		202 (2 RCTs)	⊕⊕○○ Low ^{b,c}	Women in the intervention group may have a longer mean induction to expulsion interval
Surgical intervention	2 per 100	6 per 100 (1 to 55)	RR 3.0 (0.32–27.89)	102 (1 RCT)	⊕○○○ Very low ^d	We are uncertain of the effect—the certainty of the evidence is very low
Safety (SAEs)						
(B) Oral (intervention) misoprostol vs vaginal misoprostol (comparison): Elhassan 2008,²⁵ Fadalla 2004,¹⁷ Feldman 2003,¹⁸ Kurshid 2009,²⁶ and Usmani 2013²²						
Complete abortion (24 h)	79 per 100	61 per 100 (54 to 70)	RR 0.78 (0.68–0.89)	300 (2 RCTs)	⊕⊕○○ Low ^e	In the intervention group there may be fewer women with complete abortion within 24 h
Complete abortion (48 h)	70 per 100	65 per 100 (54 to 79)	RR 0.93 (0.77–1.13)	200 (1 RCT)	⊕○○○ Very low ^{e,f}	We are uncertain of the effect—the certainty of the evidence is very low
Induction to expulsion (h)		The mean interval was 3.65 h longer (–2.87 to +10.17)		605 (5 RCTs)	⊕○○○ Very low ^{b,c,e}	We are uncertain of the effect—the certainty of the evidence is very low
Surgical intervention	7 per 100	13 per 100 (7 to 27)	RR 1.86 (0.93–3.74)	305 (3 RCTs)	⊕○○○ Very low ^{e,f}	We are uncertain of the effect—the certainty of the evidence is very low
Safety (SAEs)						
	0 per 72	0 per 71		143 (2 RCTs)		We are uncertain of the effect—the effect estimate could not be estimated
(C) Vaginal misoprostol (intervention) vs sublingual misoprostol (comparison): Elhassan 2008²⁵ and Rahimi-Sharbat 2015²⁷						
Complete abortion (24 h)	97 per 100	90 per 100 (82 to 99)	RR 0.93 (0.85–1.03)	230 (2 RCTs)	⊕⊕○○ Low ^{c,e}	There may be little or no change in the number of women with complete abortion within 24 h
Complete abortion (48 h)	99 per 100	97 per 100 (92 to 100)	RR 0.98 (0.93–1.04)	130 (1 RCT)	⊕⊕○○ Low ^{c,e}	There may be little or no change in the number of women with complete abortion within 48 h
Induction to expulsion (h)		The mean interval was 3.4 h longer (1.65 to 5.15)		100 (1 RCT)	⊕⊕○○ Low ^{c,e}	Women in the intervention group may have a longer mean induction to expulsion interval
Surgical intervention	19 per 100	22 per 100 (11 to 43)	RR 1.17 (0.59–2.33)	130 (1 RCT)	⊕○○○ Very low ^{c,e}	We are uncertain of the effect—the certainty of the evidence is very low
Safety (SAEs)						
						No direct evidence identified

Abbreviations: CI, confidence interval; RR: relative risk; SAEs, serious adverse events.

^aThe confidence interval (95% CI) around the effect estimate indicates both a positive and negative effect.

^bGRADE explanation: Downgraded one level in certainty due to inconsistency.

^cGRADE explanation: Downgraded one level in certainty due to imprecision.

^dGRADE explanation: Downgraded three levels in certainty due to very serious imprecision.

^eGRADE explanation: Downgraded one level in certainty due to unclear risk of bias.

^fGRADE explanation: Downgraded two levels in certainty due to serious imprecision.

4 | DISCUSSION

The present systematic review included 16 studies that focused on medical management of second trimester IUD. Although the certainty of the evidence in this review is limited for many outcomes, our results provide insight that may guide future management. While we identified limited evidence surrounding the added value of mifepristone, several trials reported on various dosages, routes, and preparations of misoprostol using misoprostol alone. For misoprostol alone regimens, our analyses suggest that a regimen of 400 µg misoprostol every 4 hours, administered sublingually or vaginally, may be effective. Although included trials reported few SAEs, the evidence surrounding safety was limited and we are therefore unable to conclude about group differences for the safety outcome.

Strengths of this systematic review include an exclusive focus on IUD cases and that the certainty of the evidence was assessed for each comparison and outcome by GRADE. Including only studies where IUD cases were evenly distributed and the mean gestational age fell within 14–28 weeks strengthens the validity of our results. This systematic review also has limitations. The certainty of the evidence was in general low or very low for many outcomes, mainly owing to the existence of few trials with relatively small sample sizes and unclear risk of bias. The trials showed statistical heterogeneity as well as imprecision, and outcomes were defined differently across trials. Additionally, few trials reported on IUD separately or provided disaggregated data upon request making the actual sample size of IUD cases small owing to mixed study populations. Nevertheless, few systematic reviews have focused on medical management of second trimester IUD and this review may provide valuable information with regard to management and future research needs.

WHO recommends a combination of mifepristone and misoprostol for the management of first and second trimester induced abortion in viable pregnancies.²⁹ Findings from a recently updated review on the management of fetal death below 24 weeks by Lemmers et al.,³⁰ suggest that the mifepristone–misoprostol regimen is equally effective to misoprostol alone. However, the data on which these findings are based do not include any cases of second trimester IUD. In the present review, the certainty of evidence concerning combined regimens was very low, hence we are uncertain about its benefits in the management of second trimester IUD. Our analyses suggest that there may be a small advantage of adding mifepristone 36–48 hours prior to misoprostol, but further research is needed to establish this effect. Nevertheless, the effectiveness demonstrated for combined regimens when used for other indications,⁵ together with our analysis, suggests that the advantage of a combined regimen also may apply to second trimester IUD.

When mifepristone is not available or feasible, misoprostol can be used alone.²⁹ When misoprostol is used alone our analyses suggest that 400 µg misoprostol is more effective compared with lower doses and that women receiving 400 µg experience fewer adverse effects. When comparing 400 µg with 600 µg, we found that there may be little to no difference in completeness, but that the higher dose results in a slightly shorter expulsion interval. Our analysis suggests that the 600-µg dose also leads

to more adverse effects; however, we are uncertain about the effect on adverse effects for this comparison owing to very low certainty evidence. Thus, the 400-µg dose may be the lowest dosage at which effectiveness is relatively high and the rate of adverse effects relatively low.

Our results indicate that there may be an advantage to using a loading dose of misoprostol followed by 200 µg misoprostol compared with 200 µg misoprostol alone. However, when comparing a loading dose followed by 200 µg misoprostol with 400 µg misoprostol alone, differences in effectiveness were diminished. While we may not know the true effect regarding adverse effects owing to limited certainty of evidence, our analyses suggest adverse effects also improve when the loading dose is not administered, rendering the loading dose unnecessary.

Evidence extrapolated from studies on second trimester induced abortion suggests that a shorter interval of misoprostol dosing of 3 hours compared with 6 hours is more effective and does not compromise safety.⁵ Included trials in our review used treatment intervals ranging from 2 to 12 hours but no trials compared timing of misoprostol. The dose of 400 µg, which we found to be superior in terms of effectiveness and adverse effects, was administered every 4 hours. Although this may be a reasonable interval, research is needed to establish whether this interval is ideal.

While effectiveness data may vary across routes, women value choice as it relates to their abortion experience.²⁹ Choice can include several components of the abortion experience, including route of administration. We found that the sublingual route was more effective and led to fewer adverse effects than the oral route. When comparing the sublingual and vaginal route we found that there may be little to no difference in effectiveness. Similar findings have been reported in previous systematic reviews,^{6,8,30} although Lemmers et al.³⁰ found that the sublingual route may lead to more diarrhea and pain. In contrast, Dodd and Crowther⁷ found evidence suggesting that the sublingual route is more effective than both the vaginal and oral route. Reasons for diverging results could lie in differences in gestational limits and inclusion of medications other than mifepristone and misoprostol compared with our review. It could also be because comparisons of routes in the present review sometimes included different doses and treatment intervals. Even with divergence in review results, the choice of sublingual versus vaginal route may be guided by women's preference, as substantial differences in effectiveness have yet to be demonstrated.

The uterus becomes more sensitive to prostaglandins with increasing gestational age,⁴ but reports of severe complications such as uterine rupture after use of misoprostol are extremely rare.³¹ This review included 60 women with prior uterine incision out of a total of 1890 women and no cases of uterine rupture were reported. Eight SAEs were reported by two trials; however, most trials reported no SAEs or did not report on safety at all. Included trials were also not powered to detect group differences in safety. Although SAEs were rare, and medical abortion medications are generally safe,^{4,29,31} we cannot conclude on safety in this review due to limited certainty of evidence. Furthermore, our data were limited in gestations above 24 weeks; thus, generalization of our findings to IUD above 24 weeks should be made with caution.

Our primary outcomes were effectiveness measured by completeness, expulsion time, and need for surgical intervention. It is important

to understand what value women place on such outcomes. While most of the studies included did not report on acceptability, Bracken et al.²⁴ provide key insights into women's preferences; women preferred a higher dose of misoprostol, despite increasing adverse effects, possibly due to greater effectiveness. More information is needed to better understand the trade-offs considered and made by women, especially as they relate to these outcomes and the existence of adverse effects.

In conclusion, this review provides information related to the dose, route, and preparation of misoprostol in misoprostol-only regimens. We are uncertain about the added benefit of mifepristone to misoprostol. Our findings suggest that a regimen of 400 µg misoprostol every 4 hours, administered sublingually or vaginally, may be effective in the management of second trimester IUFD. We are unable to draw any conclusions regarding safety and acceptability owing to limited evidence.

Future research focusing on management of IUFD should include IUFD only, allow for specific analyses of IUFD, as well as subanalyses by gestational age, and further explore combined regimens. Moreover, future studies should provide greater detail when reporting on various outcomes, including clear definitions, and how and when outcomes are determined.

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AUTHOR CONTRIBUTIONS

AC and AL conceived the idea and conducted the search, screening, data extraction, and quality assessments. MSF conducted the analyses and GRADE. All authors carried out the interpretation of the data, revised the article, and approved the final version for publication.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Reported side effects and satisfaction - Comparison of different misoprostol-mifepristone regimens.

Table S2. Reported side effects and satisfaction - Comparison of different dosages of misoprostol.

Table S3. Reported side effects and satisfaction - Comparison of loading doses vs. no loading dose.

Table S4. Reported side effects and satisfaction - Comparison of route of misoprostol.

Table S5. Comparison of different preparations of misoprostol when misoprostol is used alone.

Table S6. Comparison of complex regimens of misoprostol when misoprostol is used alone.

Appendix S1. Search strategy (as searched in Pubmed).