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Medical treatment for early fetal death (less than 24 weeks) (Review)

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[Intervention Review]

Medical treatment for early fetal death (less than 24 weeks)

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ABSTRACT

Background

In most pregnancies that miscarry, arrest of embryonic or fetal development occurs some time (often weeks) before the miscarriage occurs. Ultrasound examination can reveal abnormal findings during this phase by demonstrating anembryonic pregnancies or embryonic or fetal death. Treatment has traditionally been surgical but medical treatments may be effective, safe, and acceptable, as may be waiting for spontaneous miscarriage. This is an update of a review first published in 2006.

Objectives

To assess, from clinical trials, the effectiveness and safety of different medical treatments for the termination of non-viable pregnancies.

Search methods

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (24 October 2018) and reference lists of retrieved studies.

Selection criteria

Randomised trials comparing medical treatment with another treatment (e.g. surgical evacuation), or placebo, or no treatment for early pregnancy failure. Quasi-randomised studies were excluded. Cluster-randomised trials were eligible for inclusion, as were studies reported in abstract form, if sufficient information was available to assess eligibility.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We assessed the quality of the evidence using the GRADE approach.

Main results

Forty-three studies (4966 women) were included. The main interventions examined were vaginal, sublingual, oral and buccal misoprostol, mifepristone and vaginal gemeprost. These were compared with surgical management, expectant management, placebo, or different types of medical interventions were compared with each other. The review includes a wide variety of different interventions which have been analysed across 23 different comparisons. Many of the comparisons consist of single studies. We limited the grading of the quality of evidence to two main comparisons: vaginal misoprostol versus placebo and vaginal misoprostol versus surgical evacuation of the uterus.

Risk of bias varied widely among the included trials. The quality of the evidence varied between the different comparisons, but was mainly found to be very-low or low quality.

Vaginal misoprostol versus placebo

Vaginal misoprostol may hasten miscarriage when compared with placebo: e.g. complete miscarriage (5 trials, 305 women, risk ratio (RR) 4.23, 95% confidence interval (CI) 3.01 to 5.94; low-quality evidence). No trial reported on pelvic infection rate for this comparison. Vaginal misoprostol made little difference to rates of nausea (2 trials, 88 women, RR 1.38, 95% CI 0.43 to 4.40; low-quality evidence), diarrhoea (2 trials, 88 women, RR 2.21, 95% CI 0.35 to 14.06; low-quality evidence) or to whether women were satisfied with the acceptability of the method (1 trial, 32 women, RR 1.17, 95% CI 0.83 to 1.64; low-quality evidence). It is uncertain whether vaginal misoprostol reduces blood loss (haemoglobin difference > 10 g/L) (1 trial, 50 women, RR 1.25, 95% CI 0.38 to 4.12; very-low quality) or pain (opiate use) (1 trial, 84 women, RR 5.00, 95% CI 0.25 to 101.11; very-low quality), because the quality of the evidence for these outcomes was found to be very low.

Vaginal misoprostol versus surgical evacuation

Vaginal misoprostol may be less effective in accomplishing a complete miscarriage compared to surgical management (6 trials, 943 women, average RR 0.40, 95% CI 0.32 to 0.50; Heterogeneity: $Tau^2 = 0.03$, $I^2 = 46\%$; low-quality evidence) and may be associated with more nausea (1 trial, 154 women, RR 21.85, 95% CI 1.31 to 364.37; low-quality evidence) and diarrhoea (1 trial, 154 women, RR 40.85, 95% CI 2.52 to 662.57; low-quality evidence). There may be little or no difference between vaginal misoprostol and surgical evacuation for pelvic infection (1 trial, 618 women, RR 0.73, 95% CI 0.39 to 1.37; low-quality evidence), blood loss (post-treatment haematocrit (%) (1 trial, 50 women, mean difference (MD) 1.40%, 95% CI -3.51 to 0.71; low-quality evidence), pain relief (1 trial, 154 women, RR 1.42, 95% CI 0.82 to 2.46; low-quality evidence) or women's satisfaction/acceptability of method (1 trial, 45 women, RR 0.67, 95% CI 0.40 to 1.11; low-quality evidence).

Other comparisons

Based on findings from a single trial, vaginal misoprostol was more effective at accomplishing complete miscarriage than expectant management (614 women, RR 1.25, 95% CI 1.09 to 1.45). There was little difference between vaginal misoprostol and sublingual misoprostol (5 trials, 513 women, average RR 0.84, 95% CI 0.61 to 1.16; Heterogeneity: $Tau^2 = 0.10$, $I^2 = 871\%$; or between oral and vaginal misoprostol in terms of complete miscarriage at less than 13 weeks (4 trials, 418 women), average RR 0.68, 95% CI 0.45 to 1.03; Heterogeneity: $Tau^2 = 0.13$, $I^2 = 90\%$). However, there was less abdominal pain with vaginal misoprostol in comparison to sublingual (3 trials, 392 women, RR 0.58, 95% CI 0.46 to 0.74). A single study (46 women) found mifepristone to be more effective than placebo: miscarriage complete by day five after treatment (46 women, RR 9.50, 95% CI 2.49 to 36.19). However the quality of this evidence is very low: there is a very serious risk of bias with signs of incomplete data and no proper intention-to-treat analysis in the included study; and serious imprecision with wide confidence intervals. Mifepristone did not appear to further hasten miscarriage when added to a misoprostol regimen (3 trials, 447 women, RR 1.18, 95% CI 0.95 to 1.47).

Authors' conclusions

Available evidence from randomised trials suggests that medical treatment with vaginal misoprostol may be an acceptable alternative to surgical evacuation or expectant management. In general, side effects of medical treatment were minor, consisting mainly of nausea and diarrhoea. There were no major differences in effectiveness between different routes of administration. Treatment satisfaction was addressed in only a few studies, in which the majority of women were satisfied with the received intervention. Since the quality of evidence is low or very low for several comparisons, mainly because they included only one or two (small) trials; further research is necessary to assess the effectiveness, safety and side effects, optimal route of administration and dose of different medical treatments for early fetal death.

PLAIN LANGUAGE SUMMARY

Medical treatment for early fetal death (less than 24 weeks)

What is the issue?

A miscarriage is the spontaneous death and/or expulsion of an embryo or fetus from the uterus before it is able to survive on its own. This natural death of an embryo or fetus ('non-viable pregnancy' or 'intrauterine fetal death', depending on the duration of pregnancy) can be identified by ultrasound before symptoms like blood loss and abdominal pain occur. Sometimes an embryo may not have even developed ('empty sac'). In the past, treatment for a deceived embryo/fetus, has usually been by dilatation and curettage (D&C) surgery, but drugs have now been developed to replace the need for surgery which may be helpful for the expulsion to happen. Misoprostol and gemeprost are synthetic prostaglandin E analogues that can stimulate expulsion of the embryo/fetus from the uterus. Mifepristone blocks the activity of progesterone, a hormone that supports pregnancy. These and similar drugs may be useful in bringing on expulsion in women with a non-viable pregnancy and can be used before 24 weeks' gestation.

Waiting for spontaneous expulsion is also possible. Women who retain the dead embryo/fetus can experience severe blood loss or develop an infection of the womb. These are rare complications. Gastro-intestinal side effects such as nausea and diarrhoea, cramping or abdominal pain and fever have been reported with misoprostol.

Why is this important?

Surgical treatment has the disadvantage of requiring anaesthesia. It carries risks of damage to the uterus or cervix and possible development of fibrous tissue in the inner lining of the uterus. These can be avoided if the non-viable pregnancy is treated with medication, or if the woman is able to wait for a spontaneous expulsion.

We set out to determine if medical treatment is as good as, or better than, surgical treatment or expectant management (waiting for the expulsion to happen). Furthermore, we compared different doses and administration routes in order to detect which regimen most often induces a complete miscarriage with the fewest side effects.

What evidence did we find?

For this updated review, 43 randomised clinical trials involving 4966 women with non-viable pregnancies at less than 24 weeks' gestation were included. The main interventions examined were vaginal, sublingual, oral and buccal misoprostol, mifepristone and vaginal gemeprost. These were compared with surgical management, expectant management, placebo, or different types of medical interventions were compared with each other. Fourteen comparisons had only one trial. The studies varied in risk of bias. The quality of the evidence ranged from very low or low for most comparisons.

Vaginal misoprostol may hasten miscarriage when compared with placebo but made little difference to rates of nausea, diarrhoea or to whether women were satisfied with the acceptability of the method. It is uncertain whether vaginal misoprostol when compared to placebo reduces blood loss or pain because the quality of the evidence for these outcomes was found to be very low.

Vaginal misoprostol was less effective in accomplishing a complete miscarriage compared to surgical management and may be associated with more nausea and diarrhoea. Vaginal misoprostol made little difference to pelvic infection, blood loss, pain or women's satisfaction/ acceptability of method when compared to surgical management.

There was little difference between different routes of giving misoprostol when trials compared the vaginal route with placing it under the tongue or between oral and vaginal misoprostol. Single studies found mifepristone to be more effective than placebo and vaginal misoprostol to be more effective than expectant management. However the quality of this evidence was found to be very low and so we are not convinced of these findings. Mifepristone did not appear to provide any additional benefit when added to misoprostol.

What does this mean?

Using misoprostol as an alternative to surgical treatment may decrease the need for surgery for women with an early fetal death. The use of misoprostol can have some side effects such as nausea and diarrhoea, but risks of severe blood loss or pelvic infection were not higher compared to surgical treatment or expectant management. Further research is needed on drug doses, routes of administration and potential adverse effects, including future fertility, and also on women's views of drug treatment, surgery and waiting for spontaneous miscarriage.

Summary of findings for the main comparison. Vaginal misoprostol compared to placebo for early fetal death (less than 24 weeks)

Vaginal misoprostol compared to placebo for early fetal death (less than 24 weeks)

Patient or population: early fetal death (less than 24 weeks)
Setting: worldwide
Intervention: vaginal misoprostol
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vaginal misoprostol				
Complete miscarriage	Study population		RR 4.23 (3.01 to 5.94)	305 women (5 RCTs)	⊕⊕⊖⊖ LOW [1 2]	There were differences in timing of outcome measurement: after 24 hours (2 studies), after 48 hours (2 studies) or after 7 days (1 study).
	189 per 1.000	800 per 1.000 (569 to 1.000)				
Pelvic infection	Study population		not estimable	(studies)	-	
	0 per 1.000	0 per 1.000 (0 to 0)				
Nausea	Study population		RR 1.38 (0.43 to 4.40)	88 women (2 RCTs)	⊕⊕⊖⊖ LOW [3 4]	
	93 per 1.000	128 per 1.000 (40 to 409)				
Diarrhoea	Study population		RR 2.21 (0.35 to 14.06)	88 women (2 RCTs)	⊕⊕⊖⊖ LOW [3 4]	
	23 per 1.000	51 per 1.000 (8 to 327)				
Blood loss: haemoglobin difference > 10 g/L	Study population		RR 1.25 (0.38 to 4.12)	50 women (1 RCT)	⊕⊖⊖⊖ VERY LOW [5 6]	
	160 per 1.000	200 per 1.000				

		(61 to 659)			
Pain (opiate use)	Study population		RR 5.00 (0.25 to 101.11)	84 women (1 RCT)	⊕⊖⊖⊖[4 6] VERY LOW
	0 per 1.000	0 per 1.000 (0 to 0)			
Woman's satisfaction/acceptability of method	Study population		RR 1.17 (0.83 to 1.64)	32 women (1 RCT)	⊕⊕⊖⊖ LOW [6]
	750 per 1.000	878 per 1.000 (622 to 1.000)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

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

[1] Serious indirectness: differences in medication regimens used between the included studies. However: very strong association; dose-response relation (-1).
[2] Serious risk of bias: problems with blinding in various studies, downgraded because of limitation in study design (-1).
[3] Serious imprecision: only two studies with relatively few patients (-1).
[4] Serious risk of bias: unclear allocation concealment (-1).
[5] Serious risk of indirect evidence: haematocrit difference was used to estimate the amount of blood loss (-1).
[6] Serious imprecision: only one study included, wide confidence interval (-2).

Summary of findings 2. Vaginal misoprostol compared to surgical evacuation of uterus for early fetal death (less than 24 weeks)

Vaginal misoprostol compared to surgical evacuation of uterus for early fetal death (less than 24 weeks)

Patient or population: early fetal death (less than 24 weeks)
Setting: worldwide
Intervention: vaginal misoprostol
Comparison: surgical evacuation of uterus

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with surgical evacuation of uterus	Risk with vaginal misoprostol				
Complete miscarriage	Study population 921 per 1.000	368 per 1.000 (295 to 460)	RR 0.40 (0.32 to 0.50)	943 women (6 RCTs)	⊕⊕⊝⊝ LOW [1 2]	Blinding of patients and treating personnel was impossible due to the nature of the interventions. All studies used the same dosage of misoprostol (800 mcg).
Pelvic infection	Study population 71 per 1.000	52 per 1.000 (28 to 97)	RR 0.73 (0.39 to 1.37)	618 women (1 RCT)	⊕⊕⊝⊝ LOW [3 4]	Only 1 study included but with relatively large patient numbers.
Nausea	Study population 0 per 1.000	22 per 1.000 (1 to 364)	RR 21.85 (1.31 to 364.37)	154 women (1 RCT)	⊕⊕⊝⊝ LOW [3 4]	
Diarrhoea	Study population 0 per 1.000	41 per 1.000 (3 to 663)	RR 40.85 (2.52 to 662.57)	154 women (1 RCT)	⊕⊕⊝⊝ LOW [3 4]	
Blood loss: post-treatment haematocrit (%)	The mean blood loss: post-treatment haematocrit (%) was 35.5	mean 1.40 lower (3.51 lower to 0.71 higher)	-	50 women (1 RCT)	⊕⊕⊝⊝ LOW [3 4]	
Pain relief	Study population 213 per 1.000	303 per 1.000 (175 to 525)	RR 1.42 (0.82 t0 2.46)	154 women (1 RCT)	⊕⊕⊝⊝ LOW [4 5]	
Woman's satisfaction/acceptability of method	Study population 800 per 1.000	536 per 1.000 (320 to 888)	RR 0.67 (0.40 to 1.11)	45 women (1 RCT)	⊕⊕⊝⊝ LOW [6 7]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

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

[1] Serious risk of bias: only one study blinded the outcome assessors. All other studies were not blinded (-1).
[2] Serious inconsistency: varied sampling, different medication regimes, I^2 = 46% (-1).
[3] Serious risk of bias: no blinding of outcome assessors (-1).
[4] Serious imprecision: only one study with relatively few patients, small number of events and wide confidence intervals (-1).
[5] Serious risk of bias: high risk of selective reporting and unclear allocation concealment (-1).
[6] Serious risk of bias: high risk of bias for blinding and attrition (-1).
[7] Serious imprecision: only one study with relatively few patients (-1).

BACKGROUND

Miscarriage is the most frequent pregnancy complication with an incidence of at least 10% to 15% of all pregnancies (Grudzinskas 1995; Howie 1995; Simpson 1991). Traditionally, early non-viable pregnancies (less than 14 weeks) have been terminated by surgical evacuation. However, the use of medical treatment for early non-viable pregnancies is increasing. Later pregnancies (14 to 24 weeks) have been ended by medical induction of miscarriage (Say 2002).

Description of the condition

A miscarriage is defined as an intrauterine pregnancy demise confirmed by ultrasound or histology up to 13 weeks of gestation. There are different forms of non-viable pregnancies such as 'anembryonic pregnancies' (formerly called 'blighted ova') if no embryo has developed within the gestational sac, or 'missed abortions' if an embryo or fetus is present, but is dead. When fetal death occurs in later pregnancy (14 to 24 weeks of gestation) it is called intrauterine fetal demise.

The widespread use of ultrasound in early pregnancy for either specific reasons (for example, vaginal bleeding) or as a routine examination (Whitworth 2015) reveals 'non-viable pregnancies' destined inevitably to miscarry in due course.

Description of the intervention

Traditionally, early non-viable pregnancies (less than 14 weeks) have been terminated by surgical evacuation. Later pregnancies (14 to 24 weeks) have been ended by medical induction of miscarriage (Say 2002). Although clotting problems occasionally occur in women with prolonged retention of a dead fetus, this is rare and does not usually happen within the first month after fetal death. There are, therefore, not pressing medical reasons to terminate non-viable pregnancies. Although, anecdotally, many women favour early termination, so-called 'expectant management' (that is, awaiting spontaneous miscarriage) is a legitimate alternative and this policy should be considered in clinical care and in planning trials (Nanda 2012; Wieringa 2002). More recently, medical treatment is used as an alternative to surgical termination of non-viable pregnancies. There are various types of medical treatment that could be used as alternatives to surgical treatment; misoprostol, mifepristone, gemeprost, methotrexate or oxytocin. The drug most frequently investigated and now used is misoprostol. This drug can be administered via several different routes; oral, sublingual, vaginal and extra amniotic, and as a single drug therapy or combined with other types of medication such as mifepristone, methotrexate or oxytocin. Furthermore, the optimal dose of misoprostol is not known, and therefore different doses are used ranging from 100 mg up to 800 mg per dose.

How the intervention might work

Misoprostol is a synthetic prostaglandin E1 analogue. It is a type of medication that was first registered as treatment for peptic ulcers. It is also used as medical treatment for terminating an unwanted or non-viable pregnancy. Misoprostol ripens the cervix and causes uterine contractions. Furthermore, it is cost-effective (Costa 1993; Graziosi 2005; Norman 1991). Misoprostol could be especially useful in low-income countries, where transport and storage facilities are inadequate and the availability of uterotonic agents and blood is limited. Its use in obstetrics and gynaecology has been explored, especially to induce first and second trimester abortion (Ashok 1998; Bugalho 1996), for the induction of labour (Alfirevic 2014; Hofmeyr 2010) and for the prevention of postpartum haemorrhage (Tunçalp 2012), despite the fact that it has not been registered for such use. The sensitivity of the uterus for misoprostol increases with the duration of pregnancy. Though the optimal dose for the induction of first or second trimester miscarriage is not known, and remains a subject of interest in the included studies.

Dinoproston is a natural prostaglandin E2. It advances uterine contraction and also ripens the cervix, though its exact mechanism is not known. Other uterotonic drugs include ergometrine (while it acts at alpha-adrenergic, dopaminergic and serotonin receptors, it exerts on the uterus a stimulant effect) and oxytocin (a synthetic nano peptide, identical to oxytocin produced by the pituitary gland, causing rhythmic contractions of the uterus).

Other uterotonic drugs that could have a role in the induction of miscarriage include ergometrine, oxytocin,

The progesterone antagonist, mifepristone, is of value in terminating early unwanted pregnancies and may be useful in non-viable pregnancies and spontaneous miscarriage (Baulieu 1986, Kovacs 1984), alone or in combination with prostaglandin (Cameron 1986). Methotrexate has been researched for medical treatment of ectopic pregnancy and might have a place in the treatment of intrauterine non-viable pregnancies as well.

Why it is important to do this review

The use of medical treatment in termination of non-viable pregnancies is increasing. Since miscarriage is the most frequent complication of pregnancy it is important to have knowledge about the different types of medical treatment, their (cost) effectiveness and their side effects.

The initial protocol for this review aimed to combine trials of medical treatments for both non-viable pregnancies and for incomplete miscarriage but on further reflection, this was illogical. Non-viable pregnancies contain viable trophoblast (placental) tissue, which produces hormones, which may in theory make these pregnancies more susceptible to anti-hormone therapy and more resistant to uterotonic (stimulating uterine contractions) therapy than pregnancies in which (incomplete) miscarriage has already taken place. This review will therefore focus exclusively on non-viable pregnancies, before miscarriage. Another review assesses trials of medical treatments after miscarriage has occurred (Kim 2017). A further review compares expectant management with surgical treatment for miscarriage (Nanda 2012).

Our review was first published in 2006. It was last edited and published online on January 21, 2009. Since the publication of the review in 2006, multiple new clinical trials concerning medical treatment of early fetal death have been conducted, and results published. The review therefore needed to be updated.

OBJECTIVES

To assess, from clinical trials, the effectiveness and safety of different medical treatments for the termination of non-viable pregnancies.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials comparing a medical treatment with another treatment (for example, surgical evacuation), or placebo, or no treatment to terminate non-viable pregnancies. Quasi-randomised studies were excluded. Cluster-randomised trials were eligible for inclusion, as were studies reported in abstract form, if sufficient information was available to assess eligibility.

Types of participants

Women with non-viable pregnancies (i.e. where the embryo or fetus had died in utero, and in whom miscarriage would have happened inevitably in due course) if less than 24 weeks estimated gestational age. If applicable, subgroup analyses were performed for women in first and women in the second trimester (up to 24 weeks of gestational age) of pregnancy. Since different studies might use different cut-off values to consider a pregnancy in its second trimester (varying between 12 and 15 weeks of gestational age), in the subgroup analysis the exact gestational age that was used in the included studies is mentioned.

Types of interventions

Trials were considered if they compared medical treatment with other methods (for example, expectant management, placebo or any other intervention including surgical evacuation). Comparisons between different routes of administration of medical treatment (for example, oral versus vaginal), or between different drugs or doses of drug, or duration or timing of treatment, were also included if data existed.

Types of outcome measures

Trials were considered if any of the following outcomes were measured.

Primary outcomes

1. Complete miscarriage (i.e. no pregnancy tissues remaining in uterus - based on clinical findings at surgery or ultrasound examination, or both after a specific period or an uncomplicated follow-up period, or both without the need for additional surgical intervention).
2. Death or serious complications (e.g. uterine rupture, uterine perforation, hysterectomy, organ failure, intensive care unit admission).

Secondary outcomes

1. Blood transfusion.
2. Haemorrhage.
3. Blood loss (measured amount of blood, post-treatment haemoglobin or post-treatment haematocrit, or both).
4. Days of bleeding.
5. Pain (relief) (defined as: 1. differences in pain scores between the different treatment methods and/or 2. the increase or decrease in pain score after a certain treatment) and/or 3. incidence of pain as a complaint and/or 4. the use of pain medication after a certain treatment).
6. Pelvic infection (defined by the authors as fever most likely caused by pelvic infection or documented pelvic infection, or both).
7. Cervical damage.
8. Digestive disorders (nausea or vomiting or diarrhoea).
9. Hypertensive disorders.
10. Time to expulsion.
11. Duration of stay in hospital.
12. Psychological effects.
13. Subsequent fertility.
14. Woman's satisfaction/acceptability of method.
15. Costs.

Search methods for identification of studies

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

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (24 October 2018).

The Register is a database containing over 24,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link.

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

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. 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.

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

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (24 October 2018) for unpublished, planned and ongoing trial reports using the search terms given in Appendix 1.

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, *see* Neilson 2006.

For this update, the following methods were used for assessing the reports that were identified as a result of the updated search.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. Potential trials were assessed for eligibility according to the criteria described in the 'Eligibility criteria' section above. If study eligibility needed to be further clarified we contacted the investigators to request further information. Studies published in abstracts only were assessed in the same way as full-text papers. If there was sufficient information presented in the abstract to demonstrate that it met the eligibility criteria, it was included in analyses. Otherwise it was excluded with reasons noted in the Characteristics of excluded studies table.

We resolved any disagreement through discussion or, if required, we consulted a third review author.

Data extraction and management

Data were extracted from each relevant publication using a data collection form.

In addition to the main outcome measures listed above, information on the setting of the study (country, type of population, socioeconomic status), the method of randomisation, a detailed description of the regimen used (drug(s), route, dose, frequency), definitions of the outcomes (if provided), and whether or not clinicians and participants were 'blind' to treatment allocated, were collected. Furthermore, any information on completeness of follow-up was collected as well. Also, we collected the key conclusions of the included studies as reported by their authors.

For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third review author.

Data were imported in Review Manager software (RevMan 2014), and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving a third assessor.

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

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

We assessed the 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), if during data extraction we found that the trial was quasi-randomised we excluded it from further analysis;
- unclear risk of bias.

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

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

We assessed the methods as:

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

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

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

We assessed the methods as:

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

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

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

We assessed methods used to blind outcome assessment as:

- 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 described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and

exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- 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);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

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

We assessed 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; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

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

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

For this update the quality of the evidence was assessed 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 and if applicable secondary outcomes for the main comparisons (with a maximum of seven outcomes). The following outcomes were assessed.

1. Complete miscarriage
2. Pelvic infection
3. Nausea
4. Diarrhoea
5. Blood loss
6. Pain (relief)
7. Woman's satisfaction/acceptability of method

These outcomes were assessed (if applicable) for all 23 comparisons. The most clinically meaningful comparisons are presented in (Summary of findings for the main comparison; Summary of findings 2); these were:

1. vaginal misoprostol versus placebo;
2. vaginal misoprostol versus surgical evacuation.

We used the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create the 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced 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.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we use the mean difference if outcomes are measured in the same way between trials. In future updates, if applicable, we will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

Our protocol stated that we would include cluster-randomised trials in the analyses along with individually-randomised trials. We planned to adjust their standard errors using the methods described in the *Handbook* (Section 16.3.6) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we used ICCs from other sources, we planned to report this and to conduct sensitivity analyses to investigate the effect of variation in the ICC. If we had identified both cluster-randomised trials and individually-randomised trials, we planned to synthesise the relevant information. We would 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. No cluster-randomised trials were included in this update.

Cross-over trials

It is unlikely that cross-over designs would be a valid study design for this particular review, and so were expected to be excluded. In the unlikely event that cross-over trials would have a valid design and were eligible for inclusion in the review, we would use specific methods for 'Risk of bias' assessment and analysis as described in the *Handbook* (Section 16.4).

Other unit of analysis

It was likely that we would identify trials with more than two treatment groups, for example, trials comparing surgical, medical and expectant management of non-viable pregnancies. If so, we first determined which intervention groups addressed the review objective. If applicable, pair-wise comparisons of interventions were included in the appropriate analysis.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, 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.

For all outcomes, analyses were carried out, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. If we identified substantial heterogeneity (above 30%), we tried to explore it by subgroup analysis.

Assessment of reporting biases

We planned to investigate reporting biases (such as publication bias) using funnel plots. We would have assessed funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment we planned to perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average of the range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If heterogeneity was identified we checked if there were clinical subgroups of interest; and if there were, that would be the main reason to perform subgroup analysis. We considered whether an overall summary was meaningful, and if it was, used random-effects analysis to produce it.

Separate comparisons were made of different drug regimens, grouped where appropriate by number of doses given and the route of administration. Furthermore, subgroup analyses were made for comparisons that included studies with variation in dosages of medication, time in between different administrations and/or time until follow-up examination; and subgroup analyses of first versus second trimester pregnancies were performed. All of these mentioned differences might influence the chance of successful outcome. For example: in later gestational age (second trimester pregnancies), the prostaglandin receptors are more developed and therefore the outcomes of interventions with a same dosage of misoprostol could differ between first and second trimester. Another example: when different routes of administration are assessed, the dosage and whether repeat dosages are applied might influence the outcome, which means these should be considered as different subgroups of interest.

The primary and secondary outcomes used in subgroup analysis were the same as the outcomes used in the overall analysis.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this made any difference to the overall result.

RESULTS

Description of studies

Results of the search

See: Figure 1. We retrieved 162 trial reports to assess from the database searching (52 new reports, plus 108 that were already awaiting further classification, and two that were ongoing in the previous version of the review (Neilson 2006). In addition, we found three more published reports from following up clinical trial registry records (we subsequently excluded these trials as it was clear from the full report that they were not eligible). Of the 165 reports we assessed, we included 21 new trials (27 reports), excluded 112 (124 reports) and six are ongoing trials. We also added one new trial report to a previously included study, and seven new reports to previously excluded studies.

Figure 1. Study flow diagram.

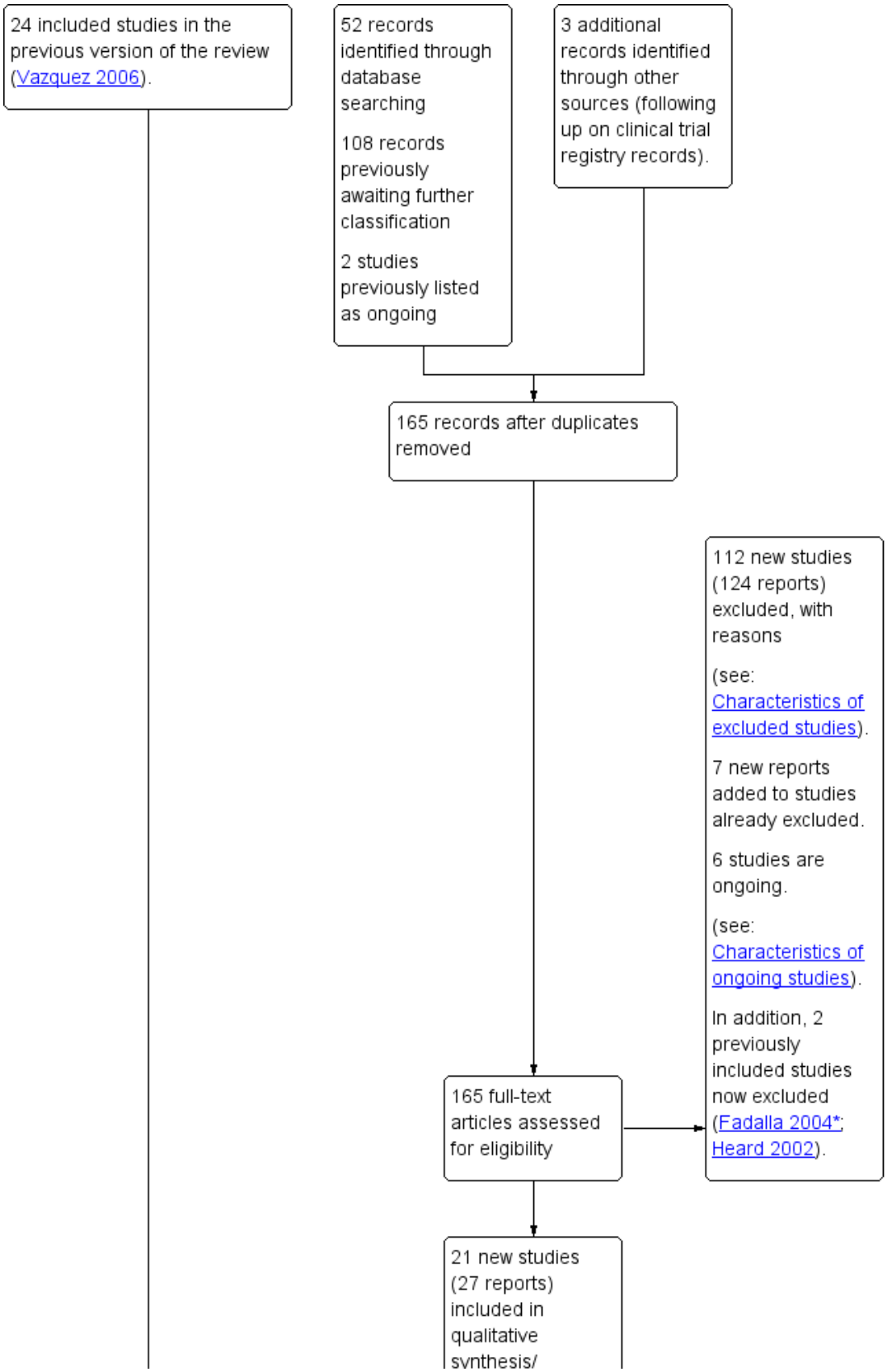
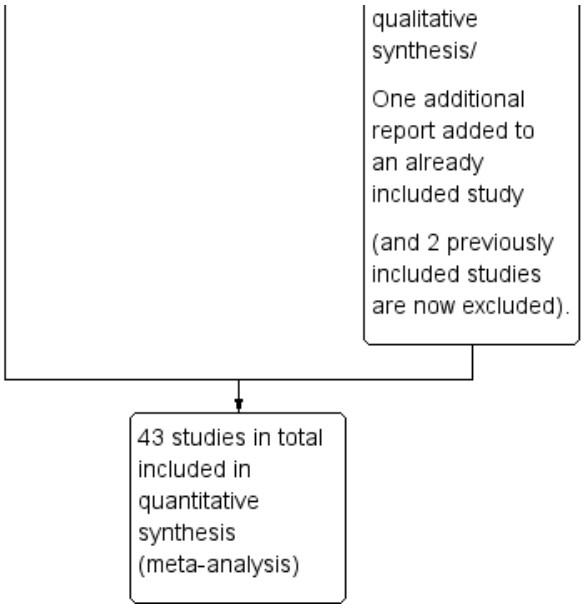


Figure 1. (Continued)



The original review included 24 studies. One of these studies was published as an abstract (Heard 2002). Since there were serious concerns about the methodology and no full-text article was published, this study was excluded from the updated review. We also reassessed and excluded another previously included study (Fadalla 2004*).

The review now has 43 included studies.

Included studies

This review has included 43 studies comparing vaginal misoprostol versus expectant management (Trinder 2006), placebo (Bagratee 2004; Herabutya 1997; Kovavisarach 2002; Lister 2005; Wood 2002), surgical evacuation (Demetroulis 2001; Fang 2009; Ganguly 2010; Graziosi 2004; Muffley 2002; Trinder 2006), oral or sublingual misoprostol (Chittacharoen 2003*; Creinin 1997; Dehbashi 2016; Marwah 2016; Ngoc 2004; Rita 2006; Shah 2010*; Sonsanoh 2014; Tang 2003; Tanha 2010a), other types of vaginal or intracervical prostaglandin preparation (Al Inizi 2003; Eng 1997*; Kara 1999*); oxytocin (Abediasl 2016*); extra-amniotic preparations (Mitwaly 2016*); different doses (Kovavisarach 2005; Mizrachi 2017; Niromanesh 2005*; Petersen 2013) and preparations (Gilles 2004) of vaginal misoprostol; the addition to vaginal misoprostol of methotrexate (Autry 1999) or laminaria tents (Jain 1996*). Furthermore, there were studies comparing sublingual misoprostol versus oral misoprostol (Ayudhaya 2006; Kushwah 2009); different doses (Tang 2006) and preparations (Saichua 2009) of sublingual misoprostol; and one study on buccal misoprostol in different doses (Bracken 2014*). Studies using other types of medication other than (only) misoprostol involved mifepristone versus placebo (Lelaidier 1993); mifepristone plus oral misoprostol versus expectant management (Nielsen 1999); mifepristone plus oral misoprostol versus misoprostol alone (Fang 2009 Schreiber 2018; Sinha 2018); and vaginal gemeprost versus surgical evacuation (Egarter 1995).

The Bagratee 2004 trial used a comparison of vaginal misoprostol versus placebo to explore comparisons with expectant management (up to seven days) and, therefore, differed in concept from the Herabutya 1997 and Wood 2002 studies in which early surgical intervention occurred after, respectively, 24 and 48 hours.

Eight of the 43 included studies addressed medical treatment of non-viable pregnancies in the second trimester. The definition of second trimester however varied from gestational age (GA) > 12 weeks to GA > 15 weeks (Abediasl 2016*; Bracken 2014*; Chittacharoen 2003*; Eng 1997*; Jain 1996*; Kara 1999*; Mitwaly 2016*; Niromanesh 2005*). One study (Shah 2010*) included women with non-viable pregnancies up to a GA of 20 weeks, but made subgroup analyses for first and second trimester pregnancies. These studies are labelled with an asterisk for ease of interpretation.

There are additional trials that included data on women with both non-viable pregnancies and incomplete miscarriages; or that included women with a GA of more than 24 weeks. We contacted several authors to ask for separated data. Four authors responded but were not able to send us the separated data (Brouns 2010; Eslamian 2007; Hidar 2005; Petrou 2006 (additional report to Trinder 2006); Promwangkwa 2017). One author responded and sent separated data (Bracken 2014*), this study was included in the review. The authors that did not respond are listed under 'Excluded studies'.

Dates of study

Included studies date from 1993 until 2018.

Funding

Among the included studies no information on funding was available in 29 trials. In 12 trials the funding was independent and mainly provided by the university hospital. One trial mentioned not to have received funding at all, and one trial mentioned to having received a donation from a pharmaceutical company for the execution of the trial.

Declaration of interest

Declaration of interest was not mentioned in 28 trials. One trial, of which the authors received a donation from a pharmaceutical company, reported this donation in their declaration of interest. The remaining 14 trials reported not to have any interests to declare.

Excluded studies

The trials that were excluded in the initial review were checked to ensure that no trial has been excluded for non-reporting of outcomes and that reasons are still valid according to current Cochrane standards. There are 162 excluded studies and these are listed in the reference section under Excluded studies. The table Characteristics of excluded studies states the reasons for exclusion from this review. These reasons mainly include: study not randomised; study including women with ongoing or incomplete miscarriage only; studies assessing medical treatment for fetal demise > 24 weeks of gestational age (GA), and studies including women having termination of pregnancy. We have also excluded studies where we tried to contact the authors for data that separates treatment of non-viable pregnancies with other types of patients (with either incomplete miscarriage, > 24 weeks, or planned termination of pregnancy), however either the authors did not respond or they were not able to provide suitable data (Behrashi 2008; Biswas 2007; Brouns 2010; Caliskan 2005; Dickinson 1998; Dickinson 2002; Elhassan 2008; El Sokkary 2016; Eppel 2005; Eslamian 2007; Fadalla 2004* Feldman 2003; Ghorab 1998; Gonzalez 2001; Grimes 2004; Herabutya 1997a; Hidar 2001; Hidar 2005; Hogg 2000; Hughes 1996; Imran 2010; Jain 1994; Jain 1999; Kurshid 2010; Kyaw 2015; Makhlouf 2003; Mostafa-Gharebaghi 2010; Nakintu 2001; Ngai 2001; Niinimaki 2006; Nuutila 1997; Owen 1999; Promwangkwa 2017 Ramsey 2004; Tanha 2013; Thavarasah 1986; Thida 2015; Toptas 2011; Torre 2012; Van Mensel 2009; Zhang 2000; Zhang 2005). Eight references turned out to be trial protocols or conference abstracts regarding studies that were also retrieved in our search and were added as additional reports to the reference of the published study results (Bracken 2014*; Lughmani 2008; Mitwaly 2016*; Nassar 2006; Nuthalapaty 2005; Stockheim 2006; Tanha 2013; Torre 2012). Sixteen studies were excluded because only a conference abstract was available and full data publication could not be retrieved (Abdel Fattah 1997; Anderman 2000; Anderson 2009; Ara 2009; Aye 2017; Chowdhury 2012; Heard 2002; Hombalegowda 2015; Linn 2015; Machtinger 2004; Nasreen 2009; Roy 2003; Shaikh 2008; Shobeira 2007; Suchonwanit 1999; Surita 1997). One study was published twice (Kushwah 2009), these two references were grouped together as one study.

Several studies turned out to be secondary analyses (cost-analyses, follow-up on fertility outcome of subsequent pregnancies, etcetera) of previous randomised controlled trials and were added as additional reports to the main references (five additional reports to Zhang 2005, two to Trinder 2006, two to Bracken 2014*, and one extra reference to respectively Elami-Suzin 2013, Niinimaki 2006 and Kovavisarach 2002). These reports however did not provide suitable additional data for meta-analysis.

Risk of bias in included studies

Please see Figure 2; Figure 3 for a summary of 'Risk of bias' assessments.

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

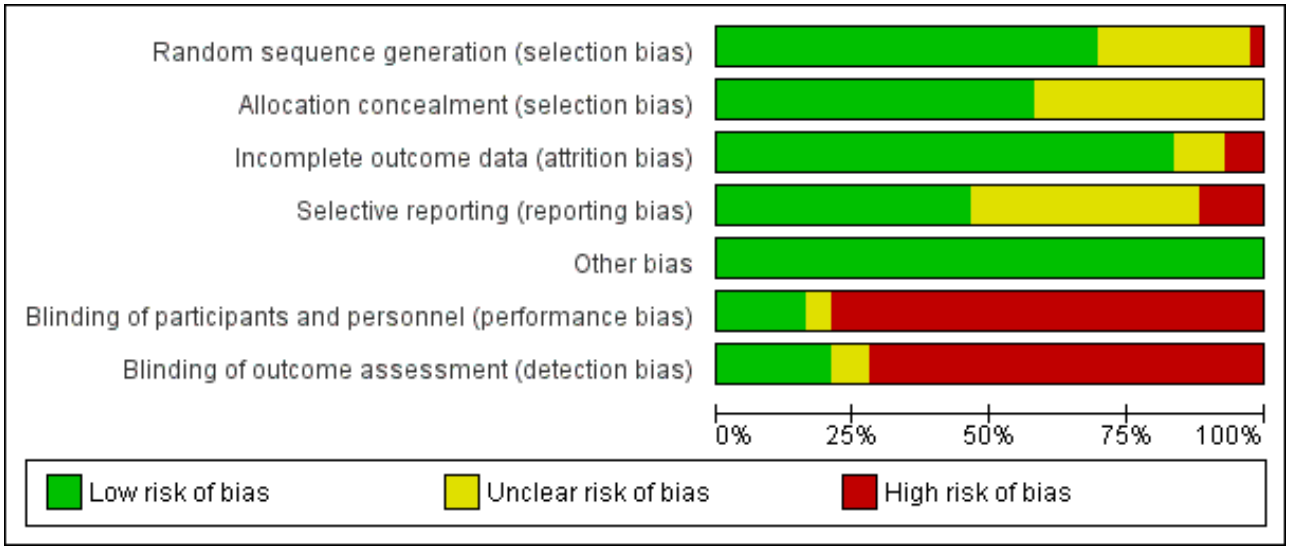


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

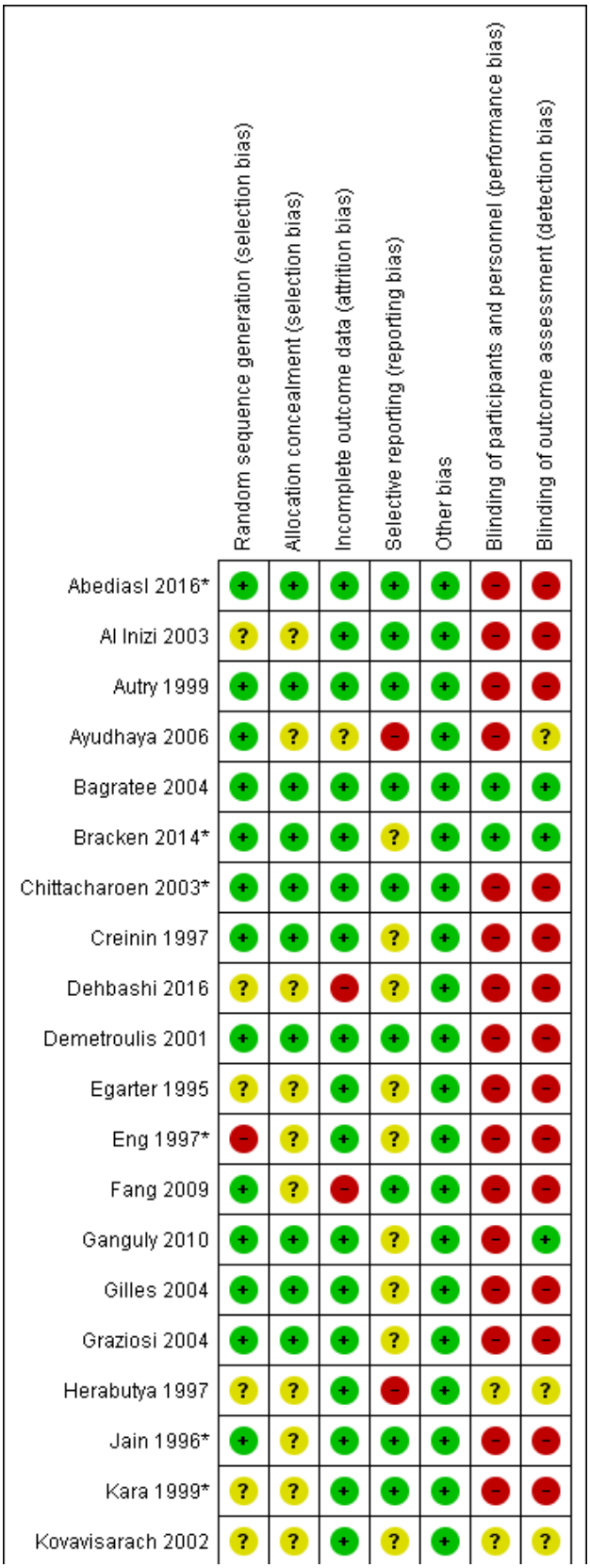
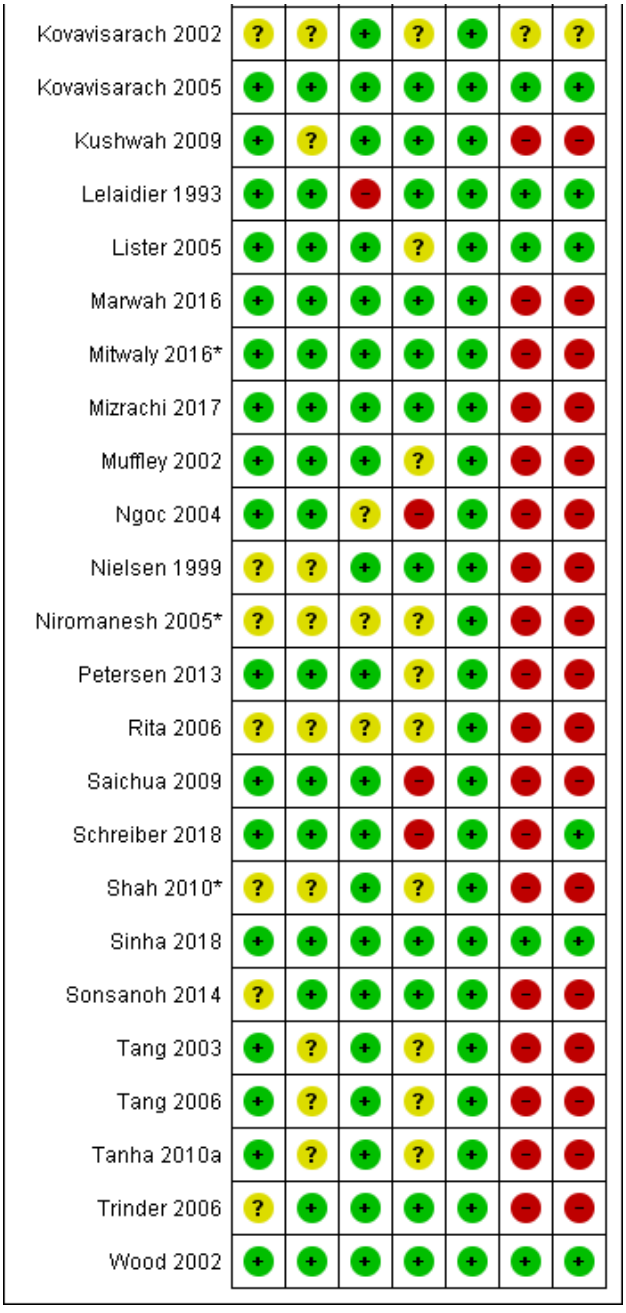


Figure 3. (Continued)



Allocation

In 30 studies the risk of bias concerning random sequence generation was assessed as being at low risk of bias (Abediasl 2016*; Autry 1999; Ayudhaya 2006; Bagratee 2004; Bracken 2014*; Chittacharoen 2003*; Creinin 1997; Demetroulis 2001; Fang 2009; Ganguly 2010; Gilles 2004; Graziosi 2004; Jain 1996*; Kovavisarach 2005; Kushwah 2009; Lelaidier 1993; Lister 2005; Marwah 2016; Mitwaly 2016*; Mizrachi 2017; Muffley 2002; Ngoc 2004; Petersen 2013; Saichua 2009; Schreiber 2018; Sinha 2018; Tang 2003; Tang 2006; Tanha 2010a; Wood 2002). These studies mainly used (computer-generated) random number tables. In one study (Eng 1997*) randomisation was carried out by "blindly picking a sealed number from a box and then odd numbers were assigned to group A (misoprostol) and even numbers to group B (gemeprost)", and so although the picking of the number from a box describes a random component to the method of sequence generation, we are unclear about the use of an odd and even number to assign thereafter. We therefore considered this as potentially high risk of bias. In the remaining 12 studies random sequence generation was not (adequately) described (Al Inizi 2003; Dehbashi 2016; Egarter 1995; Herabutya 1997; Kara 1999*; Kovavisarach 2002; Nielsen 1999; Niromanesh 2005*; Rita 2006; Shah 2010*; Sonsanoh 2014; Trinder 2006). Three studies mentioned the use of block randomisation without further description. The risk of bias was for random sequence generation was therefore considered unclear.

Twenty-five studies used robust methods of allocation concealment. Most studies used sequentially numbered sealed opaque envelopes, or numbered and sealed packets containing study medication. Furthermore, randomisation using a computer program to guarantee allocation concealment was used (Abediasl 2016*; Autry 1999; Bagratee 2004; Bracken 2014*; Chittacharoen 2003*;Creinin 1997; Demetroulis 2001; Ganguly 2010; Gilles 2004; Graziosi 2004; Kovavisarach 2005; Lelaidier 1993; Lister 2005; Marwah 2016; Mitwaly 2016*; Mizrachi 2017; Muffley 2002; Ngoc 2004; Petersen 2013; Saichua 2009; Schreiber 2018; Sinha 2018; Sonsanoh 2014; Trinder 2006; Wood 2002). For these studies the risk of bias was considered low risk for allocation concealment. Sixteen reports failed to describe the process of allocation concealment (Al Inizi 2003; Ayudhaya 2006; Dehbashi 2016; Egarter 1995; Fang 2009; Herabutya 1997; Jain 1996*; Kara 1999*; Kovavisarach 2002; Kushwah 2009; Nielsen 1999; Niromanesh 2005*; Rita 2006; Tang 2003; Tang 2006; Tanha 2010a). In these studies risk of bias for allocation concealment was unclear. This was also the case for two more studies (Eng 1997*; Shah 2010*). In these studies numbers were picked from a box, and depending on the randomness of the sequence, blinding of allocation cannot be guaranteed.

Blinding

Seven studies describe both doctors and women were blinded for the treatment allocation and used matching placebo medication to establish this (Bagratee 2004; Bracken 2014*; Kovavisarach 2005; Lelaidier 1993; Lister 2005; Sinha 2018; Wood 2002). The risk of bias was therefore considered low. Two other studies mention the use of placebo medication (Herabutya 1997; Kovavisarach 2002). It is therefore likely that women were blinded for the intervention. However the authors fail to describe if placebo tablets look similar to medication and therefore it is unsure whether doctors were also blinded for the intervention. Performance bias was unclear for these two studies. In the remaining 33 studies blinding was either not possible (due to the nature of the intervention) or not performed. In these studies performance bias was assessed high.

For the six double-blind placebo-controlled trials (Bagratee 2004; Bracken 2014*; Kovavisarach 2005; Lelaidier 1993; Lister 2005; Wood 2002) it was very likely that outcome assessors were blinded for the intervention and detection bias was therefore considered low. This was also the case for two more studies (Ganguly 2010 and Sinha 2018) which described outcome assessors were blinded for the intervention. Two more studies used placebo medication, (Herabutya 1997; Kovavisarach 2002) and it is therefore likelier that outcome assessors were blinded for the intervention. This is however not clearly described. Risk of bias was assessed as unclear for these two studies. One study describes nurses being in charge of the administration of medication (sublingual or oral misoprostol) (Ayudhaya 2006) and since doctors were the outcome assessors it could have been that they were blinded for the intervention. This is however not described. Risk of detection bias was assessed unclear in this case. In the remaining 32 studies blinding of the outcome was either not possible (due to the nature of the intervention) or not described. We considered it to be very unlikely that in these cases outcome assessors were blinded for the intervention. In these remaining 32 studies risk of detection bias was considered high.

Incomplete outcome data

Data were incomplete in at least three studies (Dehbashi 2016; Fang 2009; Lelaidier 1993). In these studies women were allocated to a specific treatment, and then wrongfully excluded from analysis. Risk of bias was considered high for these studies. In four more studies risk of attrition bias was unclear (Ayudhaya 2006; Ngoc 2004; Niromanesh 2005*; Rita 2006). For these studies lost to follow up was < 10%, secondary outcomes were not available for all included women, or failed to report on loss to follow-up. In the remaining 36 studies risk of attrition bias was considered low, because primary outcomes were available for nearly all included women.

Selective reporting

Five studies (Ayudhaya 2006; Herabutya 1997; Ngoc 2004; Saichua 2009; Schreiber 2018) had inconsistencies in outcome reporting and showed evidence of omission of outcomes in results. Furthermore, there was one study mentioning that several secondary outcomes were not reported in this paper. It was unclear whether these outcomes were reported elsewhere. These studies were considered to have a high risk on reporting bias. For 18 studies (Bracken 2014*; Creinin 1997; Dehbashi 2016; Egarter 1995; Ganguly 2010; Gilles 2004; Graziosi 2004; Kovavisarach 2002; Lister 2005; Muffley 2002; Niromanesh 2005*; Petersen 2013; Rita 2006; Shah 2010*; Tang 2003; Tang 2006; Tanha 2010a) reporting bias was unclear due to the problem that all studies reported on outcomes that were not prespecified in the method section. It was therefore impossible to assess whether all outcomes were reported upon. One study (Egarter 1995) failed to present a clear description of primary and secondary outcomes in the methods section which makes it difficult to give a judgment on selective reporting and the risk was therefore also labelled as unclear. Risk of reporting bias was considered low in 19 studies that reported on all outcomes that were mentioned in their method section.

Other potential sources of bias

For none of the included studies other potential sources of bias were detected.

Effects of interventions

See: **Summary of findings for the main comparison** Vaginal misoprostol compared to placebo for early fetal death (less than 24 weeks); **Summary of findings 2** Vaginal misoprostol compared to surgical evacuation of uterus for early fetal death (less than 24 weeks)

Forty-three studies, with a total of 4966 women, were included. Twenty-two of the studies addressed termination of non-viable pregnancies before 14 weeks. There were few reports of serious adverse effects in the reported trials, but one woman required a bowel resection after uterine perforation at evacuation of the uterus (Egarter 1995).

Subgroup analyses

For a number of comparisons with subgroups of clinical interest, extra subgroup analyses were carried out. These included the following.

For comparison 1: vaginal misoprostol versus placebo; primary outcome complete miscarriage:

1. complete miscarriage less than one day;
2. complete miscarriage less than two days;
3. complete miscarriage less than seven days.

For comparison 6: vaginal misoprostol wet versus dry preparations: primary outcome complete miscarriage:

1. complete miscarriage less than three days;
2. complete miscarriage less than eight days;
3. complete miscarriage less than 15 days;
4. complete miscarriage less than 30 days.

For comparison 8: vaginal misoprostol plus laminaria tents versus vaginal misoprostol alone: primary outcome complete miscarriage:

1. complete miscarriage less than one day;
2. complete miscarriage less than two days.

For comparison 18: buccal misoprostol lower versus higher regimen: primary outcome complete miscarriage 13 to 23 weeks:

1. complete miscarriage less than one day;
2. complete miscarriage less than two days.

For comparison 19: mifepristone versus placebo: primary outcome complete miscarriage:

1. complete miscarriage less than two days;
2. complete miscarriage less than three days;
3. complete miscarriage less than four days;
4. complete miscarriage less than five days.

All results per comparison are mentioned in the following paragraphs.

1. Vaginal misoprostol versus placebo

Primary outcomes

Treatment with vaginal misoprostol hastens miscarriage (passage of products of conception, whether complete or incomplete) when compared with placebo: miscarriage less than 24 hours (2 trials, 138 women, risk ratio (RR) 4.73, 95% confidence interval (CI) 2.70 to 8.28) miscarriage less than 48 hours (2 (other) trials, 84 women, RR 5.74, 95% CI 2.70 to 12.19); complete miscarriage without need for surgical intervention at seven days (1 trial, 83 women, RR 2.99, 95% CI 1.80 to 4.99). For these five studies combined (total of 305 women) RR of successful evacuation with misoprostol compared to placebo was 4.23, 95% CI 3.01 to 5.94; low-quality evidence; Analysis 1.1. In the GRADE assessment, the risk of bias was considered as serious because several studies lacked (information) on blinding. Furthermore, there was serious indirectness since there were differences in timing of outcome measurement: after 24 hours (two studies), after 48 hours (two studies) or after seven days (one study) which might have influenced the incidence of successful outcome, though effect of the outcome was considered large. The quality of evidence was therefore assessed as low (Summary of findings for the main comparison). In one study, one women in the placebo group had a uterine perforation after surgical evacuation was performed (1 trial, 84 women, RR 0.33, 95% CI 0.01 to 7.96) (Herabutya 1997) (Analysis 1.2).

Secondary outcomes

There was no difference in the need for blood transfusion (1 study, 84 women, RR 0.20, 95% CI 0.01 to 4.04), no difference in haemoglobin level after treatment (1 study, 50 women, RR 1.25, 95% CI 0.38 to 4.12; very-low quality evidence) or duration of bleeding (in days) (1 study, 32 women, RR 1.00, 95% CI 0.41 to 2.45; Analysis 1.3; Analysis 1.4; Analysis 1.5). There was no increase in adverse effects: nausea (2 trials, 88 women, RR 1.38, 95% CI 0.43 to 4.40; low-quality evidence), diarrhoea (2 trials, 88 women, RR 2.21, 95% CI 0.35 to 14.06; low-quality evidence; Analysis 1.6; Analysis 1.7). In one small study (Herabutya 1997), two out of 42 women used opiates for pain relief when treated with misoprostol, compared to 0 out of 42 women in the placebo group (1 trial, 84 women, RR 5.00, 95% CI 0.25 to 101.11; very-low quality evidence; Analysis 1.8). According to one study a similar number of women (58%) who would choose the same treatment strategy in the future (Graziosi 2004); although more women who had complete miscarriage after misoprostol (76%) would choose this treatment than those who required subsequent curettage (38%) (1 trial, 32 women, RR 1.17, 95% CI 0.83 to 1.64; low-quality evidence; Analysis 1.9). For all these secondary outcomes there were some limitations in study design, with unclear allocation concealment for some studies, there was evidence of 'imprecision' with small numbers of studies and wide CIs contributing to effect estimates and also some evidence of indirectness for one study (see Summary of findings for the main comparison).

The following secondary outcomes were not reported in the trials for this comparison: haemorrhage; pelvic infection; cervical damage; hypertensive disorders; time to expulsion; duration of stay in hospital; psychological effects; subsequent fertility; and costs.

2. Vaginal misoprostol versus expectant management

Primary outcomes

One study was included (614 women); in which a complete miscarriage (described as no need for additional intervention) occurred more often after misoprostol treatment compared to expectant management (RR 1.25, 95% CI 1.09 to 1.45; Analysis 2.1). The quality of this evidence in GRADE assessment was downgraded because of serious risk of bias (only one study included, no blinding performed) and serious imprecision; and was therefore assessed as low.

Death or serious complications were not reported in the trial.

Secondary outcomes

Although the total number of events was low, in the misoprostol group more infections occurred within eight weeks after study entry compared to the expectant management group (1 study, 618 women, RR 8.05, 95% CI 1.87 to 34.72; Analysis 2.2); in the included trial (Trinder 2006) infections were defined as two or more of purulent vaginal discharges, pyrexia more than 38.0°C, tenderness over the uterus on abdominal examination, and a white cell count above 15x10^9/L. Risk of bias was considered serious since no blinding was performed, and there was serious imprecision with very wide CIs because of few events in the treatment arms. The GRADE certainty of evidence is therefore considered low.

The following secondary outcomes were not reported in the trials for this comparison: blood transfusion; haemorrhage; blood loss; days of bleeding; pain (relief); cervical damage; digestive disorders (nausea or vomiting or diarrhoea); hypertensive disorders; time to expulsion; duration of stay in hospital; psychological effects; subsequent fertility; woman's satisfaction/acceptability of method; and costs.

3. Vaginal misoprostol versus surgical evacuation of uterus

Primary outcomes

Complete miscarriage was lower after initial misoprostol treatment compared to primary surgical treatment (6 studies, 943 women, average RR 0.40, 95% CI 0.32 to 0.50; low-quality evidence; Heterogeneity: Tau²0.03 I^2 = 46%; Analysis 3.1). The GRADE certainty of evidence was assessed as low; there was a serious risk of bias with no blinding performed in all studies but one and concerns due to inconsistency, but the effect was large and there were no other serious risks (Summary of findings 2). Though in the women who were treated successfully with misoprostol, surgery could be avoided. One study reported on uterine perforation (Graziosi 2004), and occurred in one woman (1 trial, 154 women, RR 0.32, 95% CI 0.01 to 7.65; Analysis 3.2).

Secondary outcomes

One study (Muffley 2002) assessed blood loss in women treated with vaginal misoprostol compared to surgical evacuation, and showed no difference in haematocrit level post treatment % (1 study, 50 women mean difference (MD) -1.40, 95% CI -3.51 to 0.71; low-quality evidence; Analysis 3.3). The use of pain relief was similar among women treated with vaginal misoprostol and surgical evacuation (1 study, 154 women, RR 1.42, 95% CI 0.82 to 4.46; low-quality evidence; Analysis 3.4). The rate of infections less than eight weeks after study entry was similar (1 trial, 618 women, RR 0.73, 95% CI 0.39 to 1.37; low-quality evidence; Analysis 3.5). Misoprostol treatment was associated with more nausea (1 trial, 154 women, RR 21.85, 95% CI 1.31 to 364.37; low-quality evidence) and diarrhoea (1 trial, 154 women, RR 40.85, 95% CI 2.52 to 662.57; low-quality evidence; Analysis 3.6; Analysis 3.7). Woman's satisfaction was not better when treated with curettage compared to misoprostol (1 study, 45 women, RR 0.67, 95% CI 0.40 to 1.11; low-quality evidence; Analysis 3.8). The quality of evidence was low because of serious risk of bias concerns, some inconsistency with varied sampling and different medication regimens and much of the data for outcomes were from single studies with wide CIs (see Summary of findings 2). In one trial (Graziosi 2004), one women in the surgical evacuation group developed Asherman syndrome.

The following secondary outcomes were not reported in the trials for this comparison: blood transfusion; haemorrhage; cervical damage; hypertensive disorders; time to expulsion; duration of stay in hospital; psychological effects; subsequent fertility; and costs.

4. Vaginal misoprostol versus vaginal dinoprostone

Primary outcomes

Vaginal misoprostol is more effective to achieve a complete miscarriage than vaginal dinoprostone for pregnancies < 14 weeks as well as > 14 weeks (2 trials, 125 women, RR 1.83, 95% CI 1.37 to 2.46; Analysis 4.1). However there was a very serious risk of bias with no information on randomisation method in the included studies, no information on allocation concealment, and no blinding. The quality of the evidence was therefore considered very low.

Death or serious complications were not reported in the trial.

Secondary outcomes

In the misoprostol group, two women needed blood transfusion (1 trial, 60 women, RR 6.07, 95% CI 0.30 to 121.33; Analysis 4.2). The incidence of nausea was similar in the one small trial that was included in this comparison (65 women, RR 1.03, 95% CI 0.28 to 3.78; Analysis 4.3). The mean duration of hospital stay in days was lower in the misoprostol group (1 trial, 60 women, MD -2.38, 95% CI -3.36 to -1.40; Analysis 4.4). The GRADE quality of evidence for these outcomes was very low because of very serious risk of bias (no clear randomisation method, no blinding) and serious imprecision (study not powered for this outcome, wide CI).

The following secondary outcomes were not reported in the trials for this comparison: haemorrhage; blood loss; days of bleeding; pain (relief); pelvic infection; cervical damage; digestive disorders (vomiting or diarrhoea); hypertensive disorders; time to expulsion; psychological effects; subsequent fertility; woman's satisfaction/ acceptability of method; and costs.

5. Vaginal misoprostol lower versus higher-dose regimens

Primary outcomes

Vaginal misoprostol has been administered in doses of 400 mcg, 600 mcg, and 800 mcg in trials: higher-dose regimens were no more effective in producing miscarriage < 13 weeks, (2 studies, 397 women, average RR 0.82, 95% CI 0.58 to 1.14; Heterogeneity Tau² = 0.05; I^2 = 73%) or 13 to 23 weeks (1 study, 100 women, RR 1.05, 95% CI 0.87 to 1.26; Analysis 5.1; Analysis 5.2). There was risk of bias because lack of proper blinding in two of the included studies (Niromanesh 2005*; Petersen 2013), and there was serious inconsistency between the studies with differences in the gestational age (GA) of included patients (< or > 14 weeks), differences in misoprostol regimen, and differences in time to outcome measurements (24 hours, 48 hours or seven days). There seemed to be a dose-response gradient, the quality of the evidence was assessed as moderate.

Death or serious complications were not reported in the trial.

Secondary outcomes

There were no differences in nausea (2 trials, 214 women, RR 0.67, 95% CI 0.31 to 1.41) and diarrhoea (2 trials, 214 women, RR 0.54, 95% CI 1015 to 1.91) between higher- or lower-dose regimens (Analysis 5.3; Analysis 5.4). However, because the risk of bias and the inconsistencies described above at the primary outcomes; the quality of the evidence were assessed as low.

The following secondary outcomes were not reported in the trials for this comparison: blood transfusion; haemorrhage; blood loss; days of bleeding; pain (relief); pelvic infection; cervical damage; digestive disorders (nausea or vomiting or diarrhoea); hypertensive disorders; time to expulsion; duration of stay in hospital; psychological effects; subsequent fertility; and costs.

6. Vaginal misoprostol wet versus dry vaginal preparations

Primary outcomes

Based on one trial there seems no clear advantage to administering a 'wet' preparation of vaginal misoprostol compared to a 'dry' preparation; miscarriage less than three days (1 trial, 80 women, RR 1.14, 95% CI 0.85 to 1.54; Analysis 6.1). When the outcome complete miscarriage was assessed on day eight, 15 or 30 there was still no clear advantage of a 'wet' preparation compared to a 'dry' preparation. Since there was serious risk of bias with only one

study included, no blinding performed, and a small sample size, the quality was assessed as being low-quality.

Death or serious complications were not reported in the trial.

Secondary outcomes

There were no differences in diarrhoea (1 trial, 77 women, RR 1.75, 95% CI 0.89 to 3.42) and vomiting (1 trial, 77 women, RR 0.93, 95% CI 0.33 to 2.62), (Analysis 6.2; Analysis 6.3). Woman's satisfaction, as measured by whether they would wish/probably wish same treatment in the future, suggests no difference between wet and dry vaginal preparations (1 trial, 73 women, RR 1.18, 95% CI 0.93 to 1.49; Analysis 6.4). Again, the quality of the evidence was considered very low.

The following secondary outcomes were not reported in the trials for this comparison: blood transfusion; haemorrhage; blood loss; days of bleeding; pain (relief); pelvic infection; cervical damage; hypertensive disorders; time to expulsion; duration of stay in hospital; psychological effects; subsequent fertility; and costs.

7. Vaginal misoprostol + methotrexate versus vaginal misoprostol

Primary outcomes

Adding methotrexate treatment to vaginal misoprostol has not been demonstrated to be advantageous in the single small trial to address this: complete miscarriage after treatment (21 women, RR 1.13, 95% CI 0.85 to 1.50; Analysis 7.1). The quality of this evidence is very low because of very serious risk of bias (only one small study included, no blinding).

Death or serious complications were not reported in the trial.

Secondary outcomes

In the small trial with 21 women that was included in this comparison there were no differences in incidence of haemorrhage (RR 2.31, 95% CI 0.10 to 50.85; Analysis 7.2) and in pain relief (RR 0.75, 95% CI 0.25 to 2.22; Analysis 7.3); but due to the small number of participants and a serious risk of bias (no blinding) the quality of this evidence is very low.

The following secondary outcomes were not reported in the trials for this comparison: blood transfusion; blood loss; days of bleeding; pelvic infection; cervical damage; hypertensive disorders; time to expulsion; duration of stay in hospital; psychological effects; subsequent fertility; woman's satisfaction/acceptability of method; and costs.

8. Vaginal misoprostol plus laminaria tents versus vaginal misoprostol alone

Laminaria tents were not proven useful adjuncts to vaginal misoprostol during the second trimester: complete miscarriage less than 24 hours (1 trial, 38 women, RR 0.90, 95% CI 0.65 to 1.25), or 48 hours (Analysis 8.1). GRADE score on quality of the evidence was downgraded two levels because of serious risk of bias (only one small study included, no blinding) and imprecision; and was considered very low.

Death or serious complications were not reported in the trial. No secondary outcomes were reported.

9. Vaginal misoprostol versus sublingual misoprostol

Primary outcome

No differences in effects were established when comparing vaginal versus sublingual preparations of misoprostol in inducing complete miscarriage < 13 weeks, although the evidence was limited by small sample sizes and heterogeneity of the included trials (five trials, 513 women, random-effects model average RR 0.84, 95% CI 0.61 to 1.16; heterogeneity $Tau^2 = 0.10$; $I^2 = 82\%$; Analysis 9.1). One trial comparing vaginal misoprostol and sublingual misoprostol for miscarriage 13 to 23 weeks also showed no difference, and also included very limited numbers (9 women, RR 0.50, 95% CI 0.13 to 2.00). The quality of evidence was downgraded because of serious risk of bias (no blinding performed in the including studies) and therefore assessed as low.

Death or serious complications were not reported in the trial.

Secondary outcomes

Although there seemed to be no differences between vaginal and sublingual misoprostol regarding nausea (4 trials, 302 women, RR 0.42, 95% CI 0.12 to 1.44; Analysis 9.5); vomiting (2 trials, 300 women, RR 0.76, 95% CI 0.46 to 1.26; Analysis 9.6); and excessive blood loss (2 trials, 340 women, RR 0.54, 95% CI 0.15 to 1.89; Analysis 9.3) these results are based on relatively small trials with large heterogeneity. Vaginal misoprostol caused less pain than sublingual misoprostol (3 trials, 392 women, RR 0.58, 95% CI 0.46 to 0.74; Analysis 9.4); and less diarrhoea (4 trials, 472 women, RR 0.71, 95% CI 0.54 to 0.92; Analysis 9.7); because of serious risk of bias described in the primary outcome above the GRADE assessment showed a very low quality of evidence. Quality of evidence was very low because of serious risk of bias, serious imprecision and serious inconsistency with differences in GA and misoprostol regimen of the included studies).

The following secondary outcomes were not reported in the trials for this comparison: blood transfusion; haemorrhage; days of bleeding; pelvic infection; cervical damage; hypertensive disorders; time to expulsion; duration of stay in hospital; psychological effects; subsequent fertility; woman's satisfaction/acceptability of method; and costs.

10. Vaginal misoprostol versus intravenous oxytocin

Primary outcomes

Misoprostol and oxytocin had similar efficacy in inducing complete evacuation of the uterus in second trimester fetal death (1 trial, 85 women, RR 1.10, 95% CI 0.96 to 1.25; Analysis 10.1). The quality of evidence was assessed as low because of very serious risk of bias (only one small study included, no blinding).

Death or serious complications were not reported in the trial.

Secondary outcomes

The incidence of excessive blood loss was not different between the groups, however the total number of events was very low (1 trial, 85 women, RR 0.56, 95% CI 0.05 to 5.97), the quality of evidence is low because of the same reasons as described in the primary outcome) (Analysis 10.2).

No other secondary outcomes were reported.

11. Vaginal misoprostol versus vaginal gemeprost

Primary outcomes

There was no difference between vaginal misoprostol and gemeprost in the induction of miscarriage less than 24 hours for fetal death after 13 weeks (1 trial, 50 women, RR 1.24, 95% CI 0.90 to 1.70; Analysis 11.1). GRADE assessment produced a low quality of evidence because of a very serious risk of bias (no blinding, doubtful randomisation report, and some signs of selective reporting).

Death or serious complications were not reported in the trial.

Secondary outcomes

One study reported on the use of opiates for pain relief (Eng 1997*). In this study, none of the women either treated with misoprostol or gemeprost used opiates for pain relief. The incidences of vomiting and diarrhoea did not differ between the misoprostol and the gemeprost group (1 trial, 50 patients, respectively RR 3.00, 95% CI 0.13 to 70.30; RR 0.14, 95% CI 0.01 to 2.63); however the studies were relatively small (Analysis 11.3; Analysis 11.4). The quality of evidence for the outcomes which were assessed were low because of the very serious risk of bias as described previously.

No other secondary outcomes were reported.

12. Sublingual + vaginal misoprostol versus only vaginal misoprostol

Primary outcomes

Sublingual and oral misoprostol did not differ in inducing a complete miscarriage (2 studies, 238 women, RR 1.07, 95% CI 0.88 to 1.30; Analysis 12.1). There was a serious risk of bias in the two included studies (no blinding, no clear allocation concealment) and there were serious inconsistencies (differences between the included studies regarding misoprostol regimen), which was partly compensated by a dose-response gradient. The GRADE quality of evidence was therefore assessed as moderate.

Death or serious complications were not reported in the trial.

Secondary outcomes

There were no differences in abdominal pain, diarrhoea and patients satisfaction (Analysis 12.2; Analysis 12.4; Analysis 12.5). Gastro-intestinal side effects (nausea, vomiting) occurred less in the sublingual misoprostol group (2 studies, 238 women, RR 0.59, 95% CI 0.41 to 0.85; Analysis 12.3). For fever, nausea, diarrhoea and abdominal pain the quality of evidence is low because of serious risk of bias and serious inconsistencies. For patients satisfaction with treatment the quality was downgraded to very low because only one small study was included at high risk of bias for blinding.

No other secondary outcomes were reported.

13. Sublingual powdery versus sublingual compact misoprostol

Primary outcomes

According to the small trial included in this comparison there is no clear advantage of administering a powdery preparation of sublingual misoprostol compared to a compact preparation: complete miscarriage (1 trial, 54 women, RR 0.96, 95% CI 0.66 to 1.41; Analysis 13.1). Since there is only one study included in which no blinding was performed and that showed signs of selective reporting, there was a very serious risk of bias and the quality of evidence is very low.

Death or serious complications were not reported in the trial.

Secondary outcomes

The incidence of nausea/vomiting and diarrhoea was similar between the groups (Analysis 13.2; Analysis 13.3). Again, the quality of evidence is very low because of the very serious risk of bias as described in the primary outcome.

No other secondary outcomes were reported.

14. Sublingual misoprostol with versus without extended course

Primary outcomes

An extended course of daily 400 mcg misoprostol for a week after initial misoprostol treatment does not lead to more cases with complete miscarriage (1 trial, 180 women, RR 1.01, 95% CI 0.93 to 1.10; Analysis 14.1). The quality of evidence was downgraded because of a very serious risk of bias (only one small study included, no blinding performed, signs of selective reporting) which was partly compensated by a dose-response gradient, and was assessed as low.

Death or serious complications were not reported in the trial.

Secondary outcomes

The extended course of misoprostol produces more diarrhoea (1 trial, 180 women, RR 2.00, 95% CI 1.25 to 3.19; Analysis 14.5). The incidence of other side effects like nausea, vomiting and pain was not different (Analysis 14.2; Analysis 14.3; Analysis 14.4; again quality of evidence was assessed as low since these comparisons included the same trial as was described in the primary outcome).

No other secondary outcomes were reported.

15. Sublingual misoprostol versus oral misoprostol

Primary outcomes

Adding sublingual misoprostol to vaginal misoprostol does not lead to more complete miscarriages (1 trial, 80 women, RR 1.00, 95% CI 0.85 to 1.18; Analysis 15.1). In this comparison only one study was included (Tang 2003), with a small number of participants, no blinding and no allocation concealment, which means a very serious risk of bias. The GRADE quality of evidence therefore is very low.

Death or serious complications were not reported in the trial.

Secondary outcomes

While efficacy seemed not to differ, adding sublingual misoprostol to a vaginal misoprostol treatment produces more diarrhoea (1 trial, 80 women, RR 2.55, 95% CI 1.48 to 4.38, quality of evidence very low because of the reasons described above). The incidence of other side effects like nausea, vomiting and pain was no different between the groups (respectively RR 1.20, 95% CI 0.80 to 1.79; RR 0.78, 95% CI 0.32 to 1.88; RR 0.75, 95% CI 0.29 to 1.97; Analysis 15.3; Analysis 15.4; Analysis 15.6). A large proportion of women was

satisfied with either sublingual and vaginal misoprostol or vaginal misoprostol alone. There was no difference in women's satisfaction (1 study, 77 women, RR 0.99, 95% CI 0.79 to 1.25; Analysis 15.7). Again, the quality of evidence for these outcomes is very low.

No other secondary outcomes were reported.

16. Oral misoprostol versus vaginal misoprostol

Primary outcomes

Overall, oral misoprostol seemed to be less effective than vaginal misoprostol in producing complete miscarriage < 13 weeks but this was not clearly shown in the effect estimates (4 studies, 418 women, average RR 0.68, 95% CI 0.45 to 1.03; Heterogeneity Tau^2 = 0.13, I^2 = 90%). A difference was seen only with the 400 mcg oral versus 800 mcg vaginal dose in first trimester miscarriages (1 trial, 20 women, RR 0.29, 95% CI 0.10 to 0.79) and with the 400 mcg oral versus 600 mcg vaginal dose in first trimester miscarriage (1 trial, 100 women, RR 0.45, 95% CI 0.30 to 0.67; Analysis 16.1). In one trial (Chittacharoen 2003*) all participating women using oral and vaginal misoprostol had a complete miscarriage, thus both regimens were equally effective. GRADE assessment showed serious risk of bias and serious inconsistencies because of differences between the studies regarding GA, misoprostol regimen and timing of outcome measurement; and blinding was performed in non of the included studies. Since a dose-response gradient could be suspected the quality of evidence was assessed as moderate.

Death or serious complications were not reported in the trial.

Secondary outcomes

There seemed to be no differences in the incidence of vomiting (2 trials, 290 women, random-effects model average RR 0.73, 95% CI 0.11 to 4.89; Heterogeneity: Tau^2 = 1.52; I^2 = 80%), nausea (3 trials, 220 women, RR 1.18, 95% CI 0.93 to 1.48) and diarrhoea (4 trials, 410 women, RR 1.06, 95% CI 0.72 to 1.58; Analysis 16.6; Analysis 16.7; Analysis 16.8). However, oral misoprostol seemed to cause slightly more often pain than vaginal misoprostol (2 trials, 200 women, RR 1.60, 95% CI 1.01 to 2.55; Analysis 16.5). There were high (and similar) levels of satisfaction with treatment (1 trial, 198 women, RR 0.96, 95% CI 0.86 to 1.06, but the quality of evidence for this outcome is very low since only one trial was included).

No other secondary outcomes were reported.

17. Oral misoprostol + mifepristone versus expectant management

Primary outcomes

In the single study included in this comparison, there was no difference in medical treatment compared to expectant management for complete miscarriage after five days (1 study, 122 women, RR 1.08, 95% CI 0.90 to 1.30; Analysis 17.1). The quality of evidence is low because of very serious risk of bias (only one study included, no blinding performed).

Death or serious complications were not reported in the trial.

Secondary outcomes

A difference in severe blood loss could not be established between the groups (1 study, 122 women, RR 0.34, 95% CI 0.01 to 8.29) but this was based on one study with large CIs (Analysis 17.2). Furthermore, the incidence of pelvic inflammatory disease (RR 0.52, 95% CI 0.05 to 5.55; Analysis 17.5) did not differ but the total number of events for this outcome was low. Woman's satisfaction was not different for both treatment modalities (1 study, 122 women, MD 3.40, 95% CI -5.54 to 12.34; Analysis 17.6). The quality of evidence was calculated as very low in the GRADE assessment because of a very serious risk of bias and serious imprecision (only one study included, wide CIs).

No other secondary outcomes were reported.

18. Buccal misoprostol lower versus higher-dose regimen

Primary outcomes

The efficacy of a higher-dose regimen of buccal misoprostol is better than a lower dose: complete miscarriage within two days (1 study, 135 women, RR 0.76, 95% CI 0.60 to 0.96); complete evacuation less than one day (1 study, 135 women, RR 0.64, 95% CI 0.46 to 0.89; Analysis 18.1). The quality of evidence was calculated as low in the GRADE assessment because of a very serious risk of bias (only one small study included, signs of selective reporting).

Death or serious complications were not reported in the trial.

Secondary outcomes

A higher-dose regimen caused more vomiting (1 study, 135 women, RR 0.30, 95% CI 0.12 to 0.76) and diarrhoea (RR 0.40, 95% CI 0.19 to 0.82; Analysis 18.3; Analysis 18.4). The incidence of nausea was similar between the groups (RR 0.61, 95% CI 0.28 to 1.34), as well as the incidence of pain (RR 0.96, 95% CI 0.87 to 1.06; Analysis 18.2; Analysis 18.5). The quality of evidence for the secondary outcomes was low because of the reasons described above.

No other secondary outcomes were reported.

19. Mifepristone versus placebo

Primary outcomes

The single study included in this comparison found mifepristone to be more effective than placebo: miscarriage complete by day five after treatment (46 women, RR 9.50, 95% CI 2.49 to 36.19; Analysis 19.1). However the quality of this evidence is very low: there is a very serious risk of bias with signs of incomplete data and no proper intention-to-treat analysis in the included study; and serious imprecision with wide confidence intervals.

Death or serious complications were not reported in the trial.

Secondary outcomes

The incidence of vaginal bleeding before day five was higher in the misoprostol group (1 trial, 44 women, RR 3.92, 95% CI 1.89 to 8.10; Analysis 19.2). There were no major differences in the incidence of pain (1 trial, 44 women, RR 2.19, 95% CI 0.93 to 5.17; Analysis 19.3) but again the quality of evidence is very low according to the GRADE assessment, for the same reasons as described in the primary outcome.

No other secondary outcomes were reported.

20. Mifepristone + misoprostol versus misoprostol alone

Primary outcomes

Three studies were included in this comparison and showed no additional value of mifepristone for the complete miscarriage rate (3 studies 447 participants, RR 1.18, 95% CI 0.95 to 1.47; Analysis 20.1). This quality of these studies was assessed moderate, two studies were not blinded, though in one of these the outcome assessor was blinded for the intervention.

Secondary outcomes

One trial reported on the need for blood transfusion, pelvic infection, nausea and diarrhoea. Incidence of transfusion was low was similar in both groups (300 women, RR 3.04, 95% CI 0.32 to 28.90; Analysis 20.2). Similarly, incidence of pelvic infection was low and equal in both groups (300 women, RR 1.01, 95% CI 0.14 to 7.10; Analysis 20.3). Nausea and diarrhoea were more common side effects, but incidence did not differ between both groups (nausea: 300 women, RR 1.01, 95% CI 0.76 to 1.36; Analysis 20.4 and diarrhoea: 300 women, RR 0.94, 95% CI 0.66 to 1.35).

Two trials reported on woman's satisfaction. Women were more satisfied when treated with mifepristone + misoprostol compared to misoprostol alone (two trials, 135 women, RR 1.36, 95% CI 1.06 to 1.75; Analysis 20.6).

21. Vaginal gemeprost versus surgical evacuation of uterus

Primary outcomes

In the one study included in this comparison (Egarter 1995), surgical evacuation was more effective than gemeprost treatment (87 women, RR 0.80, 95% CI 0.67 to 0.96; Analysis 21.1). In the surgical group, two of 44 women underwent additional treatment, one because of persistent vaginal bleeding and one because of ambiguous histology results based on what later turned out to be a tubal pregnancy. Two patients in the surgical evacuation group had a perforation of the uterus (RR (Non-event) 1.05, 95% CI 0.97 to 1.13) (4.5%, Analysis 21.2). In the GRADE assessment, the score was downgraded because of a very serious risk of bias: no clear description of primary and secondary outcomes in the methods of the included study. There is also serious imprecision: only one small study included; especially for the secondary outcomes there are wide CI. The quality of evidence is therefore calculated as very low.

Secondary outcomes

The incidence of nausea was similar in both groups (RR 1.79, 95% CI 0.56 to 5.68; Analysis 21.3), with very low quality of evidence because of the reasons described above.

No other secondary outcomes were reported.

22. Intravaginal extraamniotic misoprostol versus vaginal misoprostol

Primary outcomes

In the one study included in this comparison (Mitwaly 2016*), women receive either misoprostol dissolved in saline through a Foley catheter (extraamniotic route) or vaginal misoprostol. There seemed to be no differences in inducing complete miscarriage (180 women, RR 1.10, 95% CI 1.00 to 1.22; Analysis 22.1). The quality of evidence was low because of a very serious risk of bias with only one study included; there was no blinding performed and there was very serious imprecision since the study was not powered for the secondary outcomes.

Death or serious complications were not reported in the trial.

Secondary outcomes

The time to expulsion (in hours) was shorter for the extra-amniotic preparation (MD -4.81, 95% CI -5.66 to -3.96; Analysis 22.6). Although incidences of diarrhoea and vomiting were similar (Analysis 22.3; Analysis 22.4); there were more complaints of nausea in the group receiving vaginal misoprostol (1 trial, 180 women, RR 1.57, 95% CI 1.33 to 1.85; Analysis 22.2). The quality of evidence for the secondary outcomes is assessed as very low because of the very serious risk of bias described in the primary outcome; and imprecision with wide CIs, especially for diarrhoea.

No other secondary outcomes were reported.

23. Vaginal misoprostol with or without extended course

Primary outcomes

In one study included in this comparison (Mizrachi 2017), women were treated with 800 mcg of vaginal misoprostol either once, or twice with an interval of four days. In the other study included (Tang 2006), women were treated with 600mcg of sublingual misoprostol every three hours on the first day. Half of the women were treated with an extended course of misoprostol: 400mcg of sublingual misoprostol from day two until day eight. There were no differences in inducing complete miscarriage (351 women, RR 1.00, 95% CI 0.92 to 1.09; Analysis 23.1). The quality of evidence is low because of a very serious risk of bias (two studies included, no blinding of outcome assessors performed).

Death or serious complications were not reported in the trial.

Secondary outcomes

There were no differences found in the incidence of nausea, vomiting and diarrhoea (Analysis 23.2; Analysis 23.3; Analysis 23.4). Fewer women required analgesia for pain in the single dose group (171 women, RR 0.84, 95% CI 0.71 to 1.00; Analysis 23.5). Patients satisfaction was similar for both treatment arms, the majority of women would probably choose this treatment again (171 women, RR 1.01, 95% CI 0.84 to 1.22; Analysis 23.6).

No other secondary outcomes were reported.

Sensitivity analyses

We had planned to perform sensitivity analyses, but since too few studies were included in any analysis to carry out meaningful sensitivity analysis, this was not performed.

DISCUSSION

Summary of main results

The majority of included trials (41/43) assessed the use of misoprostol (mainly by vaginal administration). Vaginal misoprostol is an effective treatment option for early fetal death, compared to expectant management or placebo, in effecting a complete miscarriage. Compared to surgical evacuation there are more gastro-intestinal side effects, such as nausea and diarrhoea. However surgical evacuation may have particular risks that can be

avoided by primary medical treatment (for example, perforation of the uterus, lesions of the cervix). Higher-dose regimens of vaginal misoprostol seemed not to be more effective than lower-dose regimens with a similar incidence of adverse effects. Furthermore, a repeat dose of vaginal misoprostol after a certain time period seems not to further increase the number of complete miscarriages. For vaginal misoprostol treatment, adding methotrexate or laminaria tents has no advantage. Based on one trial, a wet preparation does not seem to be more effective than dry preparations of misoprostol.

Misoprostol can be administered through different routes. The vaginal route is well studied. Other routes that were assessed in trials were sublingual, oral or buccal administrations. None of the other administration routes were superior to vaginal misoprostol.

The efficacy of vaginally or sublingually administered misoprostol is similar, but sublingual administration seems to cause more pain. Adding sublingual misoprostol to a vaginal course does not improve outcomes while it may have more side effects, especially diarrhoea. Using a powdery sublingual preparation has no advantage compared to compact tablets. Sublingual misoprostol is as effective as oral misoprostol but gives less gastrointestinal side effects.

Oral misoprostol seems to be less effective than vaginal misoprostol. For buccal administrations, a higher dose improves complete miscarriage, but may lead to more side effects.

Vaginal misoprostol has equivalent efficacy compared to prostaglandin analogues (dinoprostone, gemeprost) and (in second trimester fetal death) to intravenous oxytocin.

Other medications that were assessed in this review were mifepristone (versus placebo) and vaginal gemeprost (versus surgical evacuation). Mifepristone was more effective than placebo in inducing complete miscarriage. Treatment with vaginal gemeprost was less effective than curettage for complete miscarriage, with a similar incidence of side effects (nausea).

Overall completeness and applicability of evidence

This review comprises 23 comparisons of medication (compared to other medication or to other types of treatment) that can be used for treatment of early fetal death. Several types of preparations, routes of administration and dosages were assessed, especially for misoprostol treatment. This large heterogeneity in medication regimens makes it difficult to present robust statements on the efficacy of misoprostol in general; especially since for several comparisons the level of evidence was low or even very low. For misoprostol treatment alone, 30 different regimens were used in the included trials. Most investigated were 800 mcg of misoprostol vaginally in one dosage (eight trials), 800 mcg of vaginal misoprostol repeated once after 24 hours (six trials) or four days (one trial) and 600 mcg of oral or sublingual misoprostol repeated every three hours with a maximum of four dosages (four trials). Especially for the higher dose of vaginal misoprostol (800 mcg) and the higher dose of sublingual misoprostol (600 mcg) it is safe to say that these are effective treatment options for early fetal death. The other routes of administration and dosages require more investigation to compose more robust results.

Quality of the evidence

There were large differences in quality of evidence among the different comparisons. In 16 comparisons only one trial was included, which meant a downgrade of at least one level in the GRADE assessment for certainty of evidence. In general, the quality of evidence for comparisons that included more trials was higher than comparisons in which only one trial was included.

'Summary of findings' tables are presented for the two comparisons that we considered clinically most meaningful: vaginal misoprostol versus placebo (Summary of findings for the main comparison) and vaginal misoprostol versus surgical evacuation (Summary of findings 2). The first of these comparisons presents the results of (vaginal) medical treatment itself, while the latter presents the results for medical treatment compared to the most applied other treatment option: surgical evacuation of the uterus. Since we found no major differences in effectiveness between different routes of administration; these findings might be generalised to other routes of administration as well.

The GRADE score for vaginal misoprostol compared to placebo, was assessed as low quality for complete miscarriage, nausea and diarrhoea and for treatment satisfaction. For treatment blood loss and pain, the quality of the evidence was assessed as very low. Since no included studies for this comparison reported on pelvic infection, GRADE scores could not be established for this outcome. The main reasons for downgrading the quality of evidence were due to risk of bias concerns with unclear allocation concealment and blinding and also due to concerns regarding imprecision and indirectness of the evidence.

The quality of the evidence for the comparison vaginal misoprostol versus curettage, was assessed as low quality for all outcomes: complete miscarriage; pelvic infection; nausea; diarrhoea; blood loss; pain; and woman's satisfaction. Quality of evidence was downgraded because for these outcomes due to imprecision, with only one trial providing data for these outcomes. Furthermore, blinding was not possible due to the nature of the intervention, and reports were inconsistent.

The risk of bias varied among the included trials (Figure 2). For 12 trials randomisation procedure had an unclear risk of bias due to inadequate description of the random sequence allocation and in 16 trials allocation concealment was unclear. Improper allocation concealment might have influenced the results in these trials, especially in trials where patients and personnel were not blinded for the type of intervention. One trial (Eng 1997*) was considered to have a high risk of bias. In this trial even and odd numbers were used for sequence allocation, and this is of course not random (Figure 3). In several trials blinding would have been very difficult or even impossible due to the nature of the interventions; for example, in trials that compared medical treatment to surgical evacuation. For trials that compared vaginal versus sublingual or oral medication one could argue that the use of placebo would have been possible: one group should receive vaginal medication and oral or sublingual placebo, the other group oral/sublingual medication and vaginal placebo. This is laborious and in some cases more inconvenient for the patients, but it would have been a manner to guarantee proper blinding. Furthermore, even if blinding of patients was impossible, still the outcome assessor could have been blinded. In only eight of the 43 trials blinding of patients, personnel and/or outcome assessors was mentioned (Bagratee

2004; Bracken 2014*; Ganguly 2010; Kovavisarach 2005; Lelaidier 1993; Lister 2005; Sinha 2018; Wood 2002). In most trials outcome was assessed by performing (transvaginal) ultrasound. However, ultrasound after miscarriage might have inter- and even intra-observer variability; without blinding of the outcome assessor this imposes a risk of bias. Other concerns in risk of bias were the reporting of incomplete outcome data in three trials (Dehbashi 2016; Fang 2009; Lelaidier 1993) and signs of selective reporting in five trials (Ayudhaya 2006; Herabutya 1997; Ngoc 2004; Saichua 2009; Schreiber 2018). In 18 other trials it was unclear whether there was selective reporting; in most of these trials the methods section stated that 'adverse effects' or 'side effects' were measured without further specification, while the results section showed detailed outcomes on specific side effects, but it was unclear if that were all the effects that were measured.

Since the quality of evidence is low or very low for several comparisons, mainly because they included only one or two (small) trials; further research is necessary to assess the effectiveness, safety and side effects of medical treatment in different medication regimes.

Potential biases in the review process

We have conducted a thorough investigation but still there could be biases in the review process.

Screening for eligible articles from the updated search and data extraction was performed by at least two review authors using the prespecified set of inclusion and exclusion criteria. There were some discrepancies, but we resolved these through mutual discussion. The inclusion or exclusion of conference abstracts was discussed in detail. We decided to exclude conference abstracts that were not clearly randomised trials or did not present applicable results. Furthermore, we searched for full-text articles that might have been published on these trials, and in some cases we contacted the authors to ask for full results of their studies. Unfortunately, none of them replied thus, in the end we excluded all conference abstracts.

There were several trials that could have been useful for the review, but that included patients with a gestational age more than 24 weeks as well, or patients with induced abortion/termination of pregnancy (for example, because of congenital malformations). We contacted the authors of these trials to ask for subgroup analyses or individual data. If the authors did not respond immediately, we sent them a reminder. If still they did not respond we excluded their trial. Some articles did not provide contact details for the authors; in which case we searched for other articles from these authors to find contact details, or we tried to find them on social media (Research Gate). For most of these authors we found contact details, but none of them responded to our questions. We believe that this approach was the best in order to obtain as much information as possible; however it did not provide us with extra data except for one trial (Bracken 2014*). Not having included results from these trials (especially in comparisons where currently only one trial is included) could have biased our results in two different ways; either over- or underestimating the potential effects.

Assessment of the level of evidence was also performed by two authors, any discrepancies were resolved through discussion. We think our assessment was as thorough and complete as possible.

Agreements and disagreements with other studies or reviews

The reproductive use of misoprostol is considered in other Cochrane Reviews, for indications that include treatment of incomplete miscarriage (Kim 2017), termination of unwanted pregnancies (Kulier 2011; Say 2002), induction of labour (Alfirevic 2014; Hofmeyr 2010; Muzonzini 2004), and prevention and treatment of postpartum haemorrhage (Mousa 2014; Tunçalp 2012).

For treatment of incomplete miscarriage (Kim 2017), there appeared to be a slightly lower incidence of complete miscarriage with misoprostol in comparison to surgical evacuation (average risk ratio (RR) 0.96, 95% confidence interval (CI) 0.94 to 0.98; 15 studies, 3862 women, random-effects; very low-quality evidence) but with success rate high for both methods. Overall, there were fewer surgical evacuations with misoprostol (average RR 0.05, 95% CI 0.02 to 0.11; 13 studies, 3070 women, random-effects; very low-quality evidence) but more unplanned procedures (average RR 5.03, 95% CI 2.71 to 9.35; 11 studies, 2690 women, random-effects; low-quality evidence).

In termination of unwanted pregnancies the rate of abortions not completed with the intended method was higher in the prostaglandin group (RR 2.7, 95% CI 1.1 to 6.8) compared to surgery (Say 2002). This is in line with our finding that misoprostol is less effective than surgery. In incomplete miscarriage the cervical ostium is already open, therefore misoprostol for incomplete miscarriage might be more effective than misoprostol for fetal death. Nonetheless, for all indications misoprostol still reduces the overall number of patients that receive surgical evacuation. Since surgical evacuation has some specific risks (in our review for example, there were patients with uterus perforation or Asherman syndrome), misoprostol would be a good alternative as primary treatment.

The incidence of pelvic infection in our review was comparable to treatment of incomplete miscarriage and termination of unwanted pregnancy. Duration of bleeding was longer for medical treatment compared to surgery in termination of pregnancy (Say 2002). In our review duration of bleeding for this comparison was not assessed, but post treatment haematocrit was comparable between the groups (Analysis 3.3).

Compared to expectant management, in incomplete miscarriage there was no difference identified in the need for surgical evacuation if patients were treated with misoprostol compared to expectant management (average RR 0.62, 95% CI 0.17 to 2.26; 2 studies, 308 women, random-effects; low-quality evidence). Furthermore, there was no difference in complete miscarriage (average RR 1.23, 95% CI 0.72 to 2.10; 2 studies, 150 women, random-effects; very low-quality evidence) (Kim 2017). On the contrary, in our review misoprostol decreases the need for surgical evacuation in patients with early fetal death. In incomplete miscarriage the mechanism of miscarriage is already in motion, for example, the cervical ostium is dilated and there might be contractions of the uterus. Therefore, expectant management in incomplete miscarriage might be more effective than expectant management in early fetal death, when the ostium is closed and there are no contractions. There was no difference identified in pelvic infection between misoprostol and expectant management in incomplete miscarriage (average RR 2.42, 95% CI 0.59 to 9.98; 3

studies, 333 women; Kim 2017); while in our review incidence of pelvic infection was higher in the misoprostol group.

For termination of unwanted pregnancy, misoprostol administered orally is less effective (more failures) than the vaginal route (RR 3.00, 95% CI 1.44 to 6.24; Kulier 2011), and may be associated with more frequent side effects such as nausea and diarrhoea. This is in line with our findings. Sublingual routes in induced abortion were similarly effective compared to the vaginal route (Kulier 2011), but had higher rates of side effects; while in our review side effects were similar apart from abdominal pain. Both in our review as in the review by Kulier and colleagues, there was large variety in medication regimens; this might have influenced the incidence of side effects: higher dosages that are repeated more often might lead to a higher incidence and more severe side effects.

AUTHORS' CONCLUSIONS

Implications for practice

Available evidence from randomised trials supports the use of misoprostol as one possible option for the treatment of non-viable pregnancies before 24 weeks. In general, side effects of medical treatment were minor. There were no major differences in effectiveness between different routes of administration. Treatment satisfaction was addressed in only a few studies, in which the majority of women were satisfied with the received intervention.

There is intense interest in the reproductive uses of misoprostol because it appears a potent method for pregnancy interruption as well as being cheap and stable at room temperature. Using misoprostol as an alternative to surgical treatment for early fetal death could decrease the number of curettages, thus preventing women from the specific risks that are related to surgical intervention.

Implications for research

Ultrasound demonstration of early pregnancy failure before 14 weeks is a common problem that merits greater research effort than has occurred to date. Further research to assess the effectiveness, safety and side effects of misoprostol, including optimal route of administration and dose, should focus on the dose regimens that tend to be most effective according to our review results: vaginal or sublingual misoprostol in higher dosages. Women's views about the acceptability of medical treatment, surgical treatment and expectant management could be integral to future research protocols, as could economic assessments. Long-term outcomes, notably subsequent fertility, deserves further study in appropriately powered randomised controlled studies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abediasl 2016*

Methods	RCT. Computerised random-number generator was used for sequence generation. Participants: 85 pregnant women with confirmed IUFD who were admitted for labour induction at Shariati Hospital, Bandar Abbas, Iran, from January 2013 through January 2014.
Participants	The inclusion criteria were: pregnant women with documented IUFD, a gestational age of 15–24 weeks, and a Bishop score < 4.
Interventions	Intervention: the starting dose was 200 mcg misoprostol vaginal tablets. The tablet was wet with a drop of water for injection and inserted into the posterior fornix of the vagina using a speculum and a spatula. After 12 hours, if the conception products were not expelled and the effective uterine contractions (> 3 contractions/10 minutes) were not established, another dose of 200 mcg misoprostol vaginal tablets was inserted, reaching a maximal total dose of 400 mcg (n = 40). Control: oxytocin infusion was given in 500 cm^3 of 5% dextrose with the starting oxytocin dose of 6 mU/minute. If no effective uterine contractions were noted, the dose was increased at a rate of 6 mU/minute at 45-minute intervals to reach a maximal dose of 40 mU/minute (n = 45).
Outcomes	The primary outcome of the study was the time of induction-to-delivery interval. Secondary outcomes were the success rate (evacuation < 24 hours), duration of admission, postpartum haemorrhage and complications of labour induction.
Funding	This research was funded by the Maternal, Fetal and Neonatal Research Center, Tehran University of Medical Sciences and Hormozgan University of Medical Sciences.
Declarations of interest	The authors declare that they have no conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computerized random-number generator was used for sequence generation, which was carried out by M.S. Simple randomization was used in this study".
Allocation concealment (selection bias)	Low risk	Quote: "We used consecutive opaque envelopes for the concealment of allocation, which was performed by F.K. The envelopes were opaque when held to the light, and opened sequentially and only after the participant's name and other details".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 8 women with induction failure were analysed according an intention-to-treat principle. There was no information on lost to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section are presented in the result section.
Other bias	Low risk	No other source of bias could be detected.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The implementation of assignments was carried out by Z.A.; which is another person then the persons who performed the randomization".

Abediasl 2016* *(Continued)*

		Comment: the article does not further state whether patients and personnel were blinded, however due to the nature of the interventions blinding would be practically impossible. Not blinding of personnel might have had an impact on outcome assessment (see detection bias).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: the article does not state whether there was blinding of outcome assessment. If there was no blinding, this might have had an impact on judgment of successful outcome (empty uterus).

Al Inizi 2003

Methods	'Random allocation'. Details unknown. Study conducted at Tawam Hospital— a teaching hospital tertiary care unit in the United Arab Emirates. Duration of study not mentioned.
Participants	60 women with early non-viable pregnancies diagnosed by ultrasound.
Interventions	Vaginal misoprostol 400 mcg repeated twice a day to maximum of 1600 mcg (n = 27) vs dinoprostone (PGE2) vaginal tablets repeated at 6-hourly intervals to maximum of 36 mg (n = 33).
Outcomes	Complete miscarriage/need for surgical evacuation.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	Authors contacted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "60 women with a diagnosis of missed abortion were randomly allocated". Comment: no further information on random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 60 women were randomised; and for all 60 women outcomes were reported (table 1).
Selective reporting (reporting bias)	Low risk	Comment: there is no information on how many eligible women were counselled but refused participation. Apart from that there are no signs of selective reporting; all outcome measures mentioned in the methods section were presented in the results section.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: there is no information on blinding of participants and personnel.

Al Inizi 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: there is no information on blinding of outcome assessment.

Autry 1999

Methods	Randomisation using a random number tables. Allocation concealment was accomplished in sequentially numbered opaque sealed envelopes made available at the time of enrolment in the study. Intention-to-treat analysis. Sinai Samaritan Medical Center and the Medical College of Wisconsin; no information on study duration.
Participants	21 women diagnosed with a non-viable first trimester intrauterine pregnancy up to 49 days gestation. Evidence of non-viability included 1 of the following findings on TVS: 1) mean gestational sac diameter greater than 18 mm and no embryonic pole; 2) embryonic pole 5 mm to 10 mm without cardiac activity; 3) intrauterine gestational sac with abnormal hCG titres. Others entry criteria: 1) 18 years of age or greater; 2) closed cervix on digital exam; 3) no known intolerance or allergy to misoprostol or MTX; 4) haemoglobin of 9 g/dL or greater; 5) platelet count of 100,000/µL or greater; 6) no history of blood clotting disorders; 7) no active liver or renal disease; 8) ability and willingness to comply with visit schedule; 9) hCG less than 40,000 IU/L; and 10) easy access to a telephone and transportation.
Interventions	Combined group (n = 12): IM MTX 50 mg/m^2 body surface area (day 1) followed 2 days later (day 3) by vaginal misoprostol 800 mcg (by vaginal placement of 4 200 mcg tablets of misoprostol). If the gestational sac was present vaginal misoprostol was repeated. Misoprostol only group (n = 9): 4 200 mcg tablets placed in the vagina on day 1. The remainder of the follow-up was similar to that for combined group.
Outcomes	Successful complete abortion: MTX plus misoprostol 12/12 vs misoprostol only 8/9. No blood transfusion or antibiotics. Positive urine pregnancy test at the initial follow-up appointment: 2/9 vs 7/7. Pain relief: 4/12 vs 4/9.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	Wisconsin, Milwaukee, USA. All women received: 1) prescription for 10 tablets acetaminophen with codeine (300 mg/30 mg) and 8 tablets of ibuprofen (600 mg); 2) instruction sheet including phone number to contact physician 24 hours/day; and a diary sheet to record symptoms, side effects, and pain medication use. Data about side effects (headache, nausea and emesis) and women's satisfaction reported as no separate data. Authors conclude that both treatments are effective regimens for the complete evacuation of non-viable early first trimester pregnancy, and represent a reasonable alternative for women wishing to avoid surgery.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using a random number table for each centre".
Allocation concealment (selection bias)	Low risk	Quote: "Allocation concealment was accomplished in sequentially numbered opaque sealed envelopes made available at the time of enrolment in the study". Comment: adequate type of allocation concealment.

Autry 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: according to the results section outcomes were measured for all 21 included patients, no signs of loss to follow-up or incomplete data.
Selective reporting (reporting bias)	Low risk	Comment: no signs of selective reporting; all outcomes mentioned in the methods section were presented in the results section.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information on blinding of participants and personnel, probably not done.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessor, probably not done.

Ayudhaya 2006

Methods	Parallel randomised controlled trial. Randomisation according to computer-generated numbers. Performed in antenatal care clinic of department of Obstetrics and Gynaecology at Ramathibodi Hospital in Bangkok, Thailand. 138 women with diagnosis of early pregnancy failure were included between November 2004–December 2005.
Participants	Pregnant women with gestational age 7-12 weeks and on ultrasound: 1. intrauterine fetal sac > 2 cm without fetal pole, or 2. presence of fetal pole without cardiac activity, or gestational sac < 2 cm with no interval growth or persistent absence of fetal cardiac pulsation on rescanning after 7-10 days.
Interventions	400 mcg misoprostol sublingually every 4 hours up to 6 doses (n = 70) vs 400 mcg misoprostol orally every 4 hours up to 6 doses (n = 68).
Outcomes	Outcomes 1. Complete abortion, defined as cervical os closed, no bleeding and endometrial thickness < 1 cm; mean induction to abortion interval. 2. Secondary outcome: adverse effects (abdominal pain, diarrhoea, nausea/vomiting, fever, chills).
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: women were randomised according to computer-generated numbers.

Ayudhaya 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: outcome group: oral misoprostol 68 women were randomised after which 2 women were excluded due to incomplete hospital records. However, table 2 reports of 68 women, and not of 66 women.
Selective reporting (reporting bias)	High risk	Comment: the methods section states that primary outcome is induction-to-delivery interval; however in the results section also dichotomous success rates are mentioned (complete or incomplete abortion). There were 68 patients in the intervention group, but for only 66 patients outcome is described. Furthermore, the methods section mentions 'adverse effects' as secondary outcome without further specification. Therefore is it unclear whether the adverse effects mentioned in the results section are the only ones that were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: due to the nature of the intervention blinding would be difficult; the only way for blinding both participants and personnel would be to give group A oral misoprostol and sublingual placebo and group B oral placebo and sublingual misoprostol. The article does not state that placebos were used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: medication was administered by nurses; outcome assessment was performed by doctors according to the article. The article does not state whether these doctors were blinded for type of intervention.

Bagratee 2004

Methods	Computer-generated random allocation of study number. Numbered envelopes containing misoprostol or placebo. All women presenting to the Early Pregnancy Assessment Unit (EPAU) at St Mary's Hospital, London, UK, from August 2001 to March 2002.
Participants	104 women who attended Early Pregnancy Unit, St Mary's Hospital, with incomplete miscarriage or early pregnancy failure < 13 weeks.
Interventions	600 mcg misoprostol (n = 52) or placebo [expectant management] (n = 52). Second dose next day unless complete miscarriage had occurred in meantime. Review day 7 and surgical evacuation if miscarriage not complete. Further review at day 14.
Outcomes	Primary: complete miscarriage without need for ERPC by day 7. Secondary outcomes: clinical, side effects, satisfaction and future choices.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	Primary outcome reported for both non-viable pregnancies and incomplete miscarriages, but not for secondary outcomes. These will be added if authors can provide data separately for non-viable pregnancies and incomplete miscarriages.

Risk of bias

Bias	Authors' judgement	Support for judgement

Bagratee 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Computer-based allocation", allocation "according to the random schedule".
Allocation concealment (selection bias)	Low risk	Quote: "Three misoprostol or placebo tablets were placed in each of two small envelopes and sealed. These small envelopes were then placed in consecutively numbered larger envelopes according to the random schedule and sealed by staff not involved in the study". Comment: adequate allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The 104 women randomized to the trial attended the scheduled visits as per protocol and completed the trial". Comment: no signs of missing data.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the results section, no signs of selective reporting.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Three misoprostol or placebo tablets were placed in each of two small envelopes and sealed. These small envelopes were then placed in consecutively numbered larger envelopes according to the random schedule and sealed by staff not involved in the study". Comment: this means both patients as well as the doctor randomising the patients were unaware of the type of treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: patients and doctors randomising the patients were blinded for treatment allocation (see blinding of participants and personnel above), assuming the doctor assessing the outcome was the same as the 1 randomising the patients, there was sufficient blinding of outcome assessment.

Bracken 2014*

Methods	Double-blind randomised trial. Randomised using a simple randomisation sequence generated by computer with blocks of 10. Randomisation was stratified by study site. Montefiore Medical Center, Stanford University, Stroger Hospital, Christiana Health System, the Huong Vuong Hospital in Ho Chi Minh City, Viet Nam; from December 2008 to December 2011
Participants	Women who sought medical care for possible fetal demise in pregnancies of between 14 and 28 weeks from December 2008 to December 2011. Confirmation of fetal demise and final gestational age were determined by ultrasound.
Interventions	Intervention: 100 mcg buccal misoprostol (n = 63). Study drug was administered at 6-hourly intervals, for a maximum of 8 doses. Control: 200 mcg buccal misoprostol (n = 72). Study drug was administered at 6-hourly intervals, for a maximum of 8 doses.
Outcomes	The primary outcome was the fetal-placental delivery rate within 48 hours of misoprostol commencement without any additional intervention. Rates of success were compared across study arms.

Bracken 2014* *(Continued)*

Funding	This study was funded by a grant from the Office of Orphan Products Development of the United States Food and Drug Administration.
Declarations of interest	The authors declare no conflicts of interest.
Notes	This study included patients with gestational age > 24 weeks. We contacted the author, who could provided us with subgroup analysis for patients with gestational age < 24 weeks; therefore we were able to include this study in the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The groups were created by Gynuity Health Projects using a simple randomization sequence generated by computer with blocks of 10. Randomization was stratified by study site". Comment: this is an adequate type of random sequence generation.
Allocation concealment (selection bias)	Low risk	Comment: the article states that research assistants created packages of medication but randomisation seems to be done by doctors, there probably was allocation concealment for the doctor randomising the patient.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the flowchart shows that discontinuation was < 5%. All patients that were initially randomised were included in the analysis. Since there was no loss to follow-up and discontinuation was very low, it is likely data outcome data were complete.
Selective reporting (reporting bias)	Unclear risk	Comment: the results section presents secondary outcome measures that were not mentioned in the methods section. Unclear whether these were all the outcomes measured, or if other variables were measured but not presented.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A research assistant prepared numbered and sealed randomization packets before beginning enrolment. Each packet contained eight individually labelled dose envelopes. Each woman was administered a randomization envelope containing two tablets' (100 mcg misoprostol tablet + placebo resembling this tablet or 2 tablets of 100 mcg misoprostol)". Comment: probably the packets were handed out to the patients by other personnel than the research assistant preparing them; so there was probably blinding of both patients and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: the care taking physician was blinded for the intervention, and therefore also blinded during assessment of the outcome.

Chittacharoen 2003*

Methods	Parallel randomised controlled trial; computer-generated random numbers in sealed opaque envelopes. Department of Obstetrics and Gynaecology, Ramathibodi Hospital, Bangkok, Thailand between July 1999 and June 2001.

Chittacharoen 2003* *(Continued)*

Participants	Women at 16–41 weeks' gestation with intrauterine fetal death; subgroup analysis on gestational age 16-22 weeks available.
Interventions	Group A (n = 40) 2 tablets of 200 mcg of misoprostol orally. The progression of labour was evaluated by cervical examination before subsequent dosage at 4-hour intervals until delivery; group B (n = 40) 1 tablet of 200 mcg of misoprostol inserted high in the posterior fornix and a subsequent dose of 200 mcg at 12-hour intervals until delivery.
Outcomes	Success (complete abortion) within 48 hours.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: computer-generated random numbers in sealed opaque envelopes.
Allocation concealment (selection bias)	Low risk	Comment: sealed opaque envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcomes were presented for all 80 patients.
Selective reporting (reporting bias)	Low risk	Comment: no signs of selective reporting; al outcomes mentioned in the methods section were presented in the results section.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: due to the nature of the treatment (medication orally vs vaginally) blinding is difficult; probably not done.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no description of blinding on outcome; no statement that the doctor assessing the outcome was another person than the one randomising the patient. Probably not done.

Creinin 1997

Methods	Sealed, numbered, sequential envelopes containing instructions based on computer-generated random number table. Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Magee-Womens Hospital, Pittsburgh, Pennsylvania; no information on study duration.
Participants	20 women with non-viable pregnancies diagnosed by transvaginal ultrasound; < 9 weeks; closed cervix; no contra-indication to misoprostol; no heavy bleeding.

Creinin 1997 *(Continued)*

Interventions	400 mcg misoprostol orally, repeated after 24 hours if the pregnancy had not been expelled (n = 12); vaginal misoprostol 800 mcg - repeated after 24 hours if necessary (as above) (n = 8). Surgical evacuation offered to women in both groups after 48 hours if treatment unsuccessful.
Outcomes	Miscarriage; pain (visual analogue scale); side effects.
Funding	Supported by a grant from the Magee Women's Health Foundation.
Declarations of interest	No information on conflicts of interest.
Notes	Pilot study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using a computer-generated random number table to account for 25 patients". Comment: adequate type of random sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "The group was assigned by opening the next sequentially numbered, sealed, opaque envelope. Randomization and envelope preparation were performed by a person not directly associated with the study". Comment: adequate type of allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there is no description of missing data other than for 2 patients bHCG level was missing (which was not the primary outcome).
Selective reporting (reporting bias)	Unclear risk	Quote: 'Two subjects in group 1, upon review, did not appropriately meet the ultrasound criteria for early pregnancy failure'. Comment: apart from these 2 excluded patients; there might have been selective reporting: in the methods section is stated that side effects were measured, but no further specification. In the results section nausea, vomiting and diarrhoea were presented; unclear whether these were all outcomes that were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Neither the clinician nor the patient was blinded to the treatment group". Comment: due to the nature of the interventions blinding was practically impossible; but not blinding might have influenced outcome.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessment, probably not done.

Dehbashi 2016

Methods	Randomised clinical trial; April 2014-Nov 2014 in Amiralmomenin hospital in Zabol city (Iran).

Dehbashi 2016 *(Continued)*

Participants	Women in first trimester admitted for pregnancy termination because of fetal IUFD or missed abortion
Interventions	Sublingual misoprostol 400 mcg, repeated every 4 hours, max 5 times (n = 25); vaginal misoprostol 400 mcg, repeated every 4 hours, max 5 times (n = 27)
Outcomes	Complete miscarriage < 24 hours; secondary outcomes: side effects like nausea, diarrhoea
Funding	No information on funding.
Declarations of interest	The authors report no conflict of interest related to this paper.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned, because of small sample size, block randomization was performed according to the time of admission"
Allocation concealment (selection bias)	Unclear risk	Quote: ''Single blind allocation and intervention were conducted by a nurse"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: in sublingual group, 1 of the patients did not respond to medical abortion that underwent curettage surgery and was thus excluded. Another one had severe abdominal pain that was also excluded because on intolerability.
Selective reporting (reporting bias)	Unclear risk	Quote: "In sublingual group, one of the subjects did not respond to medical abortion that underwent curettage surgery and was thus excluded. Another one had severe abdominal pain that was also excluded because on intolerability"
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: blinding was not performed. Due to the nature of the intervention blinding was difficult; the only way to achieve this would have been to give the 'sublingual misoprostol group' vaginal placebos and vice versa.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: blinding of outcome assessment is not described.

Demetroulis 2001

Methods	Randomisation by opening sealed opaque envelope containing computer-generated allocation code number. No attempt at masking given the manifest differences between medical and surgical interventions. Newham General Hospital; no information on study duration.
Participants	80 women with incomplete miscarriage or anembryonic pregnancy or missed miscarriage < 13 weeks, diagnosed by ultrasound. The data in this review are derived only from the subgroup with non-viable pregnancies (n = 50) and not those with incomplete miscarriages. Women were reviewed 8-10 hours

Demetroulis 2001 *(Continued)*

	after medical treatment; if they had empty uteruses on ultrasound examination they were discharged home; if not, surgical evacuation was arranged.
Interventions	Vaginal misoprostol 800 mcg once only (n = 26) vs surgical evacuation of the uterus (n = 24).
Outcomes	Need for surgical evacuation, symptoms including pain and bleeding, 'satisfaction'.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	Authors contacted for information on outcomes according to indication for treatment. Only usable data currently available are on incidence of surgical evacuation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: computer-generated numbers.
Allocation concealment (selection bias)	Low risk	Comment: use of sealed opaque envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing data, it seems that all patients completed the study.
Selective reporting (reporting bias)	Low risk	Comment: no signs of selective reporting. 94 patients were counselled, 14 declined study participation and chose surgical evacuation. All outcome measures mentioned in the methods section were reported in the results section.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "No attempt was made to conceal the intervention assignment schedule from the patients or clinicians as the treatment methods for the study and control were obviously different (...) No attempt was made to mask the intervention as the study compared a medical treatment with a surgical procedure". Comment: this might have influenced (perception of) outcome.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: not performed. Quote: "No attempt was made to mask the intervention as the study compared a medical treatment with a surgical procedure".

Egarter 1995

Methods	Women quote: "randomly assigned"; no details. Department of Gynecology and Obstetrics, University of Vienna; no information on study duration.
Participants	87 women in Austria with non-viable pregnancies between 8 and 12 weeks, diagnosed by ultrasound.

Egarter 1995 *(Continued)*

Interventions	Vaginal gemeprost 1 mg every 3 hours up to maximum of 3 mg daily for 2 days (n = 43) vs uterine curettage (n = 44).
Outcomes	Need for surgical curettage. Adverse effects.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information on random sequence generation other than 'patients were randomly assigned'.
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all patients that were randomised completed the study: for all randomised patients outcome was presented.
Selective reporting (reporting bias)	Unclear risk	Comment: no clear description of primary and secondary outcomes in methods section; unclear what precise outcome measure was. Several outcomes were presented in the results section, unclear if this was all that was measured. Furthermore, it is unclear how it was measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not mentioned, probably not done.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: not mentioned, probably not done.

Eng 1997*

Methods	Randomised by quote: "blindly picking a sealed number from a box". Treatment allocation was then based on whether the number was odd or even. Hospital Kuala Lumpur Malaysia; June 1995 to January 1996
Participants	50 women with IUFD at 13-26 weeks of pregnancy.
Interventions	Vaginal misoprostol 200 mcg 3-hourly up to a maximum dose of 1200 mcg (n = 25) vs vaginal gemeprost 1 mg 3-hourly up to a maximum dose of 5 mg (n = 25).
Outcomes	Main outcome quote: "treatment failure" defined as failure to miscarry within 24 hours, or side effects severe enough to preclude use of additional dose of drug.

Eng 1997* *(Continued)*

Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Randomization was carried out by blindly picking a sealed number from a box. Odd numbers were assigned to group A (misoprostol) and even numbers to group B (gemeprost)". Comment: no information on who put the numbers in the box.
Allocation concealment (selection bias)	Unclear risk	Comment: inadequate allocation concealment; a sealed number was picked from a box; not clear if the investigators used opaque envelopes, not clear who put the numbers in the box.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: it seems that all 50 patients completed the study.
Selective reporting (reporting bias)	Unclear risk	Comment: the methods section states that 'side effects' were measured, without further specification. It is unclear whether the side effects that are mentioned in the results section were all that were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information on blinding participants and personnel, probably not done.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessment, probably not done.

Fang 2009

Methods	Women with IUFD were randomised into 3 groups. Group A (n = 30): vaginal misoprostol (MP) 0.4 mg, 3 hours before vacuum aspiration; group B (n = 30): vaginal MP 0.4 mg every 3 hours, up to 5 doses; group C (n = 30): oral mifepristone (MF) 200 mg 36 to 48 hours before vaginal MP 0.4 mg, MP was given every 3 hours, up to 5 doses. This trial covered women hospitalised for treatment on missed abortion from 2005.09.01 to 2007.02.28
Participants	Patients of missed abortion, identified via ultrasound: a) irregular intrauterine gestation sac in a max diameter > 20 mm, no embryo observed; b) impaired intrauterine gestational sac development > 1 week; c) intrauterine gestational sac > 6 mm in max diameter, embryo visualised without cardiac canal beating. 4) Impaired intrauterine gestational sac development, gestational age < 84 days (12 weeks).
Interventions	Vaginal misoprostol 400 mcg every 3 hours, up to 5 doses vs oral mifepristone 200 mg 36 to 48 hours before vaginal misoprostol 400 mcg every 3 hours up to 5 doses.

Fang 2009 *(Continued)*

Outcomes	Complete miscarriage, women's satisfaction
Funding	No information on funding
Declarations of interest	No information on conflicts of interest
Notes	Outcome was only reported for 15 of 30 women receiving vaginal misoprostol treatment. The other 15 women were excluded from the analysis because emergency curettage was performed due to blood loss.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Women enrolled were randomized (computer-generated random numbers)"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcome was only reported for 15 of 30 women receiving vaginal misoprostol treatment. The other 15 women were excluded from the analysis because emergency curettage was performed due to blood loss.
Selective reporting (reporting bias)	Low risk	All outcomes pre specified were reported
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not mentioned, probably not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: not mentioned, probably not done

Ganguly 2010

Methods	Parallel randomised controlled trial. Computer-generated random number list. The study was conducted at RG Car Medical College and Hospital, Kolkata, India between 1st May 2007 and 30th April 2008.
Participants	Anembryonic gestation or embryonic or fetal death with CRL 5 mm to 40 mm without cardiac activity; inevitable miscarriage with gestational sac < 45 mm or embryonic pole < 40 mm, open cervical os and vaginal bleeding.
Interventions	Intervention: 800 mcg misoprostol vaginally (n = 120). Control: manual vacuum aspiration under iv sedation (n = 60).
Outcomes	Success rate (complete evacuation at day 8); secondary outcomes: adverse events (haemorrhage, cervical tear/perforation, fever, nausea, diarrhoea, abdominal pain, satisfaction (would use this treatment again).

Ganguly 2010 *(Continued)*

Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	Subgroup analyses on fetal death and anembryonic gestation available; therefore the study was included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: computer-generated random number list.
Allocation concealment (selection bias)	Low risk	Comment: opaque sealed envelope.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: for all 180 patients outcome was presented.
Selective reporting (reporting bias)	Unclear risk	Comment: in the results section several outcome measures are presented that were not mentioned in the methods section; unclear whether there were more outcome measures.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: there is no information on blinding of participants and personnel. Due to the nature of the intervention blinding would have practically be impossible. However especially the secondary outcomes (experience of pain and satisfaction among the non-blinded patients) might have been influenced by type of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Outcome assessors of the study were blinded".

Gilles 2004

Methods	Random allocation by computer-automated telephone response system. Stratification by pregnancy type. Random permuted blocks of size 4 or 8. Participants were recruited from 4 clinical centres between September 2001 and February 2002.
Participants	80 women with anembryonic pregnancy < 46 mm sac diameter or embryonic/fetal death with crown-rump length < 41 mm. 4 centres.
Interventions	Quote: "Wet misoprostol" 800 mcg + 2 mL saline vaginally (n = 41) vs "dry misoprostol" (as above without saline) (n = 39). Second dose given day 3 if no miscarriage.
Outcomes	Primary outcome: miscarriage without need for curettage before 30 days. Secondary outcomes: miscarriage < 3, < 8 and < 15 days; side effects, women's views.
Funding	Supported by National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services under contracts No. N01-HD-1-3321 through 3325.

Gilles 2004 *(Continued)*

Declarations of interest	The following persons and institutions participated in the National Institute for Child Health and Human Development Management of Early Pregnancy Failure Trial (principal investigators are indicated by asterisks): J. Zhang* and T. Nansel (National Institute of Child Health and Human Development); C. Westhoff,* A. Davis, and C. Robilotto (Columbia University); J. Gilles,* J. Kang, F. Doyle, and N. Vazquez (University of Miami); K. Barnhart,* T. Bader, and K. Timbers (University of Pennsylvania); M. Creinin,* B. Harwood, R. Guido, M. Fox, L. Reid (University of Pittsburgh); and M. Frederick,* S. Forman, and X. K. Huang (Clinical Trials and Surveys Corporation). No further information on conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with a computer automated telephone response system. The subjects were stratified by pregnancy type with the use of random permuted blocks of size 4 or 8. The Data Coordinating Center developed the process for randomization".
Allocation concealment (selection bias)	Low risk	Quote: "The enrolment sequence was concealed from investigators". Comment: adequate allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 patients were lost to follow-up (both in group I) from day 15 (according to table 1); primary outcome was still measured for them before; so for primary outcome there were no incomplete data.
Selective reporting (reporting bias)	Unclear risk	Comment: some outcomes in the results section (for example, abdominal pain) were not mentioned in the methods section. Unclear how many secondary outcomes were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Neither the investigators nor the subjects were masked because the addition of saline solution made the interventions visibly different". Comment: this might have influenced the (perception of) outcome.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessment, considering that investigators and subjects were not masked for the intervention this was probably not done.

Graziosi 2004

Methods	Consent for study obtained at time of diagnosis of early pregnancy failure. Randomised after at least 1 week of expectant management. Computer programme with block randomisation sequence. Stratification by previous vaginal birth; gestational age < or > 10 weeks; centre. The study was performed in 3 teaching hospitals in the Netherlands (St Antonius Hospital Nieuwegein, St Elisabeth Hospital Tilburg and Tweesteden Hospital Tilburg) between November 2001 and June 2003
Participants	154 women with ultrasound-diagnosed early pregnancy failure - either anembryonic pregnancy or fetal death at 6-14 weeks. 6-centre study in the Netherlands.

Graziosi 2004 *(Continued)*

Interventions	Vaginal misoprostol 800 mcg; repeated after 24 hours if ultrasound indicated remaining tissue in the uterus. Curettage after 3 days if miscarriage hadn't occurred or was incomplete (n = 79) or suction curettage within a week of randomisation (n = 75).
Outcomes	Primary: complete evacuation. Secondary: side effects, pain and need for analgesia, intensity/duration of bleeding.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	Of 241 eligible women, 87 (36%) declined to participate and chose curettage.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: computer program with a block randomisation sequence.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by their treating gynaecologist using a computer program with a block randomization sequence, thus guaranteeing the concealment of allocation". Comment: adequate type of allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: flowchart (fig 1) shows detailed information on follow-up of patients. No signs of incomplete data.
Selective reporting (reporting bias)	Unclear risk	Comment: methods section states that side effects were measured, without further specification. Unclear whether the side effects that are presented in the results are all that were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information on blinding of participants and personnel, probably not done considering the type of intervention (medication vs surgical evacuation).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessment, probably not done considering the type of intervention (medication vs surgical evacuation).

Herabutya 1997

Methods	Quote: "Random allocation" but method not discussed in paper. Ramathibodi Hospital between March 1995 and April 1996, Bangkok, Thailand.
Participants	84 women with ultrasound confirmation of fetal death with uterine size < 14 weeks, no bleeding, and cervix closed.
Interventions	Misoprostol (200 mcg vaginally) (n = 42) or vaginal placebo (n = 42) on admission to hospital.

Herabutya 1997 *(Continued)*

Outcomes	Primary outcome was miscarriage within 24 hours of treatment. Some information available on complications.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	Much of the outcome data reported describes only the subgroups who did miscarry before surgical evacuation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information on random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: for all 84 randomised patients outcome was presented.
Selective reporting (reporting bias)	High risk	Comment: The methods section states that side effects were registered, but they were not reported in the results. Much of the outcome data reported describes only the subgroups who did miscarry before surgical evacuation.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information on blinding of patients and personnel. Sinces patients received either misoprostol or placebo it is likely that they were blinded, but this is not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there is no information on blinding of outcome assessment. Considering that placebo was used as comparison there might have been blinding of the outcome assessor, assuming this was not the person providing the medication (and thus capable of recognising a placebo if it had another shape than the misoprostol).

Jain 1996*

Methods	"Random number table". From the Department of Obstetrics and Gynecology, University of Southern California School of Medicine; no information on study duration.
Participants	70 women in Los Angeles, USA, with either fetal death (n = 40) or medical or genetic indications for termination of pregnancy (n = 30) at 12-22 weeks. Only data from pregnancies complicated by fetal death included here.
Interventions	Vaginal misoprostol 200 mcg 12-hourly plus laminaria tents (n = 20) vs vaginal misoprostol 200 mcg 12-hourly alone (n = 18).

Jain 1996* *(Continued)*

Outcomes	Miscarriage.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	Adverse effects are described for the groups as wholes, so are not included here. 2 women excluded from analyses - 1 protocol violation; 1 was found to have interstitial ectopic pregnancy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: use of a random number table.
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcome was described for all 38 patients. 2 patients were excluded before analyses (1 protocol violation and 1 found to have interstitial ectopic pregnancy).
Selective reporting (reporting bias)	Low risk	Comment: no signs of selective reporting.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information on blinding of patients and personnel. Due to the nature of the intervention (misoprostol with or without laminaria tents) it is unlikely that there was blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: there is no information on blinding of outcome assessment. Considering the type of treatment (laminaria tents or not) it is unlikely that there was blinding.

Kara 1999*

Methods	Quote: "Random allocation". No details. Zeynep Kamil Women and Childrens Hospital, Istanbul, Turkey. No information on study duration.
Participants	65 women in Istanbul, Turkey, with ultrasound-diagnosed fetal death in second trimester.
Interventions	Vaginal misoprostol 200 mcg (n = 32) vs intracervical dinoprostone 0.5 mg (n = 33). Intravenous oxytocin started after 6 hours if no 'effective contractions'.
Outcomes	Complete miscarriage. Adverse effects.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.

Kara 1999* *(Continued)*

Notes	Misoprostol dose reported as 200 mg. Assumed to be 200 mcg. Time to miscarriage not included as standard deviations seem incorrect.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: quote: "Random allocation". No details.
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 65 patients were randomised, for all of them outcomes were presented, there seems to be no missing data.
Selective reporting (reporting bias)	Low risk	Comment: misoprostol dose reported as 200 mg. Assumed to be 200 mcg. Other than these findings no signs of selective or unclear reporting.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information on blinding of participants and personnel, considering the type of intervention (different number and shape of tablets used) probably not done.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessment, probably not done.

Kovavisarach 2002

Methods	Quote: "Random allocation". Method not discussed. Between 1 July 1998 and 31 January 1999 at the gynaecologic clinic at Rajavithi Hospital, Bangkok, Thailand.
Participants	54 women with anembryonic pregnancies < 12 weeks diagnosed by TVS. Single centre study in Bangkok, Thailand.
Interventions	Vaginal misoprostol 400 mcg (n = 27) or placebo (n = 27). Reviewed after 24 hours and curettage offered if no or incomplete miscarriage. Further review after 1 week.
Outcomes	Primary: complete miscarriage within 24 hours of treatment.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Kovavisarach 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated". Comment: method not discussed.
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 54 women were recruited in the study, for all of them outcomes were reported.
Selective reporting (reporting bias)	Unclear risk	Comment: in the results section several side effects (nausea, pain) are reported that were not mentioned in the methods section; unclear if these were the only side effects that were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information on blinding of patients and personnel. Sinces patients received either misoprostol or placebo it is likely that they were blinded. Blinding of personnel that might recognise misoprostol if the placebo tablets had another shape remains unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there is no information on blinding of outcome assessment. Considering that placebo was used as comparison there might have been blinding of the outcome assessor, assuming this was not the person providing the medication (and thus capable of recognising a placebo if it had another shape than the misoprostol).

Kovavisarach 2005

Methods	Random allocation using sealed, sequentially numbered envelopes, prepared using published table of random numbers. Between 25 November 2002 and 31 July 2003, Rajavithi Hospital, Bangkok, Thailand
Participants	114 women in Bangkok, Thailand, with non-viable pregnancies (anembryonic or fetal deaths) at < 12 weeks, diagnosed by TVS. Women with open cervices were not eligible for recruitment.
Interventions	Vaginal misoprostol 600 mcg (n = 57) or 800 mcg (n = 57). If complete miscarriage not effected within 24 hours, or if clinical circumstances dictated (pain, bleeding), uterine curettage was performed.
Outcomes	Primary: complete miscarriage without need for uterine curettage within 24 hours. Secondary: adverse effects.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Kovavisarach 2005 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Women were randomly assigned to either dose of misoprostol using sealed sequentially numbered envelopes that had been prepared using a published table of random numbers".
Allocation concealment (selection bias)	Low risk	Quote: "The drugs had been placed in the opaque envelopes by a nurse who was not involved in any of the other study processes". Comment: adequate type of allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No women withdrew from the trial". Comment: no signs of incomplete outcome data.
Selective reporting (reporting bias)	Low risk	Comment: no signs of selective reporting, variables that were measured according to the methods section were presented in the results section.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The drugs had been placed in the opaque envelopes by a nurse who was not involved in any of the other study processes. All other staff and patients were blinded to regimen allocation". Group A received 3 tablets of misoprostol and 1 placebo, group B received 4 tablets of misoprostol.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: staff was blinded to regimen allocation.

Kushwah 2009

Methods	Parallel group randomised controlled trial. Patients were randomly assigned to 1 of 2 groups by computer-generated numbers. The study was conducted from April 2003 to March 2004 with 100 women attending the prenatal clinic of the Department of Obstetrics and Gynecology of Sucheta Kriplani Hospital, Delhi, India. All had early pregnancy failure confirmed by ultrasound between the 7th and 14th week.
Participants	The inclusion criteria were (1) a gestational sac of 25 mm in mean diameter or larger with no embryo present (an anembryonic pregnancy) or (2) the presence of a fetal pole without cardiac pulsations (a missed abortion).
Interventions	Group 1: 200 mg mifepristone + 600 mcg misoprostol sublingually; with up to 3 supplemental doses of 400 mcg after 12, 15 and 18 hours (if 4 hours after last dose still no expulsion: surgical evacuation) (n = 50). Group 2: 200 mg mifepristone + 600 mcg misoprostol orally; with up to 3 supplemental doses of 400 mcg after 12, 15 and 18 hours (if 4 hours after last dose still no expulsion: surgical evacuation) (n = 50).
Outcomes	The primary outcome was the mean induction-to-evacuation interval, defined as the time between when the first dose of misoprostol was taken and the time when the POC were expelled. The secondary outcome was the incidence of the 5 following adverse effects: blood loss, abdominal pain, nausea, vomiting, diarrhoea, and fever. Regimen acceptability was defined as whether it would be accepted again, if needed.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.

Kushwah 2009 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were then randomly assigned to one of 2 groups by computer generated numbers".
Allocation concealment (selection bias)	Unclear risk	Comment: no adequate description of the concealment process
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: for all 100 patients outcomes were presented.
Selective reporting (reporting bias)	Low risk	Comment: outcome measures that were mentioned in the methods section were presented in the results section.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: due to the nature of the intervention blinding would be difficult; the only way for blinding both participants and personnel would be to give group A oral misoprostol and sublingual placebo and group B oral placebo and sublingual misoprostol. The article does not state that placebos were used. This might particularly have influenced patients experiences that were assessed as secondary outcomes.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessment, probably not done.

Lelaidier 1993

Methods	Drug or identical placebo supplied by pharmacy using randomisation list using permutation blocks of 4. Department of Obstetrics and Gynaecology, Hopital A.Beclere, Clamart, France. Study duration 6 months, no further information.
Participants	46 women with non-viable pregnancies diagnosed by ultrasound on 2 examinations separated by 1 week. < 14 weeks. No bleeding or pain.
Interventions	Mifepristone 600 mg orally (n = 23) or placebo (n = 23). All women were reviewed after 5 days and if miscarriage had not occurred, surgical evacuation was performed that day.
Outcomes	Primary outcome was expulsion of the pregnancy. Symptoms also recorded.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	2 women in the placebo group underwent surgical evacuation by private practitioners before 5th day review. Both were in the process of miscarriage and were classed as expulsion positive; no information available on symptoms.

Lelaidier 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: drug or identical placebo supplied by pharmacy using randomisation list using permutation blocks of 4.
Allocation concealment (selection bias)	Low risk	Comment: identical placebo were used, supplied by pharmacy.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 46 patients included in this trial, two were not included in the results since contradictory advice from private clinicians ended in regular dilatation and aspiration. They both came from the placebo group and were excluded from the denominator when calculating percentages of spontaneous abortion". Comment: this is not an adequate intention-to-treat analysis.
Selective reporting (reporting bias)	Low risk	Comment: no signs of selective reporting; outcome measures mentioned in the results section were presented in the results section.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''This study was prospective, randomized and double-blind". Comment: adequate blinding by use of identical placebo in control group.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: no specific information on blinding of outcome assessment. Considering that blinding of patients and personnel was adequate, this was probably also done.

Lister 2005

Methods	Random allocation - blocked and stratified by physician office and by day of recruitment - day of diagnosis, or after day of diagnosis. Patients were enrolled between February 15,2002, and March 19, 2003 at Riverside Methodist Hospitals, Columbus, USA.
Participants	34 women in Columbus, Ohio, USA, with early pregnancy failure (anembryonic pregnancies or early fetal deaths) diagnosed by TVS.
Interventions	Vaginal misoprostol 800 mcg, repeated after 24 hours if sac still present on TVS (n = 18) or placebo (n = 16).
Outcomes	Primary: miscarriage complete at 48 hours.
Funding	Supported by Riverside Methodist Hospital Medical Research Foundation.
Declarations of interest	No information on conflicts of interest.
Notes	Planned sample size 84 but trial stopped after interim analysis of first 36 women. 2 women excluded from analysis - 1 protocol violation; 1 did not meet entry criteria. 2 women did not come for assessment 2 weeks after initial treatment.

Lister 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The study epidemiologist generated the allocation sequence. Randomization to misoprostol or placebo was blocked and stratified by physician office and timing of treatment in relation to diagnosis (on the day of diagnosis or 1-14 days after diagnosis)".
Allocation concealment (selection bias)	Low risk	Comment: opaque randomisation packets with instruction sheets and either misoprostol or matching placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 patients withdrew consent before treatment. These were not included in the analyses. All other 34 patients were analysed.
Selective reporting (reporting bias)	Unclear risk	Comment: table 3 shows side effects; these were not mentioned in the methods section. Unclear whether these were all the side affects that were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: physicians randomising and treating the patients received opaque randomisation packets containing misoprostol or matching placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: not described; but considering the treating physician was blinded for intervention, blinding of outcome assessment was probably also done.

Marwah 2016

Methods	Governmental multi-speciality hospital, Chandigarh, India from June 2013-June 2014
Participants	Women aged 18-45, gestational age < 12 weeks, diagnosis of missed abortion on ultrasound, minor vaginal blood loss, but cervical os closed. Haemoglobin level >= 9 mg/dL axillary temperature < 37.5 degree C, no history of inflammatory bowel disease, asthma, liver disease or contraindication to use of misoprostol, place of residence within 100 km from of the hospital, willingness and ability to give informed consent, willingness to abstain from intercourse for first 14 days of study
Interventions	400 mcg vaginal misoprostol (wet preparation) every 6 hours, max 3 doses (n = 50); 400 mcg oral misoprostol, every 6 hours, max 3 doses (n = 50)
Outcomes	No need for surgical evacuation (AP diameter < 15 mm) < 12 hours after last dose of misoprostol
Funding	Financial interests: none
Declarations of interest	Other competing interests: none
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Marwah 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned to one of the two regimens, using computer generated sequentially numbered envelopes"
Allocation concealment (selection bias)	Low risk	Quote: "sequentially numbered envelopes"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: data of all included women were presented
Selective reporting (reporting bias)	Low risk	Comment: no signs of selective reporting, data of all included women were presented
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: due to the nature of the intervention blinding would have been very difficult and would only be achieve by using oral placebos for the 'vaginal group' and vice versa.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: blinding of outcome assessor was not described.

Mitwaly 2016*

Methods	Randomised controlled trial, Assiut women's health hospital Egypt, 1 Feb 2015-1 Dec 2015.
Participants	Women 13-24 weeks of gestation with IUFD confirmed by ultrasound
Interventions	Intrauterine, extra-amniotic misoprostol 200 mcg in saline dissolute solution, administered through Foley catheter per 4 hours (n = 90); vaginal misoprostol 200 mcg (wet preparation) every 4 hours (n = 90)
Outcomes	Induction to (fetal) expulsion interval. Secondary: dose of misoprostol used, need for analgesics and need for surgical evacuation in cases of retained placenta and occurrence of side effects.
Funding	No information on funding.
Declarations of interest	The authors declare that they have no conflict of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A statistician prepared a computer generated random table"
Allocation concealment (selection bias)	Low risk	Quote: "...placed the allocation data in serially numbered sealed envelopes. The envelopes opened only by the clinician according to the order of attendance of women. Allocation unchanged after opening the closed envelopes"

Mitwaly 2016* *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all data on randomised women were available
Selective reporting (reporting bias)	Low risk	Comment: there are no signs of selective reporting, all pre described outcomes were presented in results
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: due to the nature of the intervention blinding of personnel nor participants was possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: blinding of outcome assessor was not described

Mizrachi 2017

Methods	Randomised controlled trial, single university affiliated tertiary medical centre, between August 2015 and June 2016
Participants	Women diagnosed with early pregnancy loss in the gynaecologic emergency room, either anembryonic gestation or embryonic death, were eligible for inclusion if pregnancy size by TVS was up to 12 weeks' gestation
Interventions	800 mcg vaginal misoprostol + 800 mcg vaginal misoprostol on day 4 (n = 84); 800 mcg vaginal misoprostol (n = 87)
Outcomes	The primary outcome was treatment success, defined as no need for surgical intervention up to Day 8. This included emergent and elective surgical interventions. Secondary outcomes were adverse effects, pain level, OTC analgesics use, treatment acceptability and the need for late intervention as reported by the participants by telephone on day 45.
Funding	The authors did not receive funding for this study
Declarations of interest	The authors declare no conflict of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "subjects were randomly assigned to either a single-dose protocol or a repeat-dose protocol in a 1:1 ratio. A blocked randomization scheme was created using a computer generated list of random numbers. Each block consisted of 30 participants."
Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation was concealed by placing assignments in sequentially numbered opaque envelopes"
Incomplete outcome data (attrition bias)	Low risk	Comment: flow chart displays all outcome data available. Missing data are explained.

Mizrachi 2017 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Comment: no signs of selective reporting, all outcomes described are presented in results
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: due to the nature of the intervention blinding would be difficult
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: blinding of outcome assessor is not described

Muffley 2002

Methods	Computer-generated random number table with blocked permutations - group assignments recorded in sealed opaque numbered envelopes. This clinical study was conducted between June 1999 and March 2000 at Naval Medical Center Portsmouth.
Participants	50 women with non-viable pregnancies diagnosed by ultrasound (anembryonic or embryonic/fetal deaths) < 12 weeks. Exclusions: excessive bleeding, anaemia, unstable vital signs, coagulopathy, asthma or other contra-indication to prostaglandin treatment, infection, open cervix.
Interventions	800 mcg misoprostol vaginally, repeated after 24 hours if ultrasound showed tissue still present in uterus; final review after further 24 hours - if tissue still present, surgical evacuation performed (n = 25). Suction curettage (n = 25).
Outcomes	Primary outcome: miscarriage.
Funding	Supported by the Chief, Navy Bureau of Medicine and Surgery, Washington DC, Clinical Investigation Program (CIP No. 99-037)
Declarations of interest	The views expressed in this article are those of the authors and do not reflect the official position of the Department of Defense, the Department of the Navy, or the United States Government
Notes	Analysis by intention-to-treat. Details about nausea, vomiting, diarrhoea reported only for misoprostol group.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: use of computer-generated random number table with blocked permutations.
Allocation concealment (selection bias)	Low risk	Comment: group assignments were recorded in sealed opaque numbered envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: '"Twenty-five women were placed randomly in the medical arm of the study, and 25 women were placed randomly in the surgical arm. 2 patients in

Muffley 2002 *(Continued)*

		the surgical arm had spontaneous pregnancy loss before their scheduled procedures. All but 2 of the subjects had a complete post procedure evaluation". Comment: this means a loss to follow up of < 10%.
Selective reporting (reporting bias)	Unclear risk	Comment: in the results section there are reports about nausea, vomiting and haemorrhage. These side effects were not mentioned in the methods section. Unclear whether these were all the side effects that were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: randomisation and envelope preparation was performed by a person not directly associated with the study.However due to the nature of the interventions (medication vs surgical evacuation) blinding would be practically impossible and was probably not done.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: there is no information on blinding of outcome assessment. Probably not done.

Ngoc 2004

Methods	Randomised by opening sequentially numbered envelope - prepared by computer-generated code in blocks of 10. Recruitment took place at Hung Vuong Hospital in Ho Chi Minh City, Vietnam, from January through August 2003.
Participants	200 women in Ho Chi Minh City, Vietnam, with non-viable first trimester pregnancies (anembryonic or early fetal death) diagnosed by ultrasound; cervix closed.
Interventions	Oral misoprostol 800 mcg (n = 100) vs vaginal misoprostol 800 mcg (n = 98). Women reviewed after 48 hours; if retained products present, they were given option of surgical evacuation or further review after another 5 days (when evacuation was performed if there were still products present).
Outcomes	Primary: complete miscarriage without need for surgical evacuation. Secondary: adverse effects.
Funding	Funding by David and Lucile Packard Foundation
Declarations of interest	No information on conflicts of interest.
Notes	2 women lost to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: the randomisation scheme was created by Population Council staff, using a computer-generated code in blocks of 10.
Allocation concealment (selection bias)	Low risk	Quote: "The study investigator opened the next sequentially numbered randomized envelope to determine the treatment arm".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Two women in the vaginal group and one in the oral group were lost to follow-up. One woman in the vaginal group was later reached by telephone".

Ngoc 2004 *(Continued)*

		Comment: table 2 shows side effects for 190 patients (not 200 patients), so there are some missing data. This was < 10% of total study population.
Selective reporting (reporting bias)	High risk	Comment: in table 2 side effects were presented for 95 patients per treatment arm, which is a sign of missing data. Analyses for these side effects were measured as an percentage of 95 women instead of 100 women. This influences the outcomes.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Neither the investigator nor the woman was blinded to the treatment assignment". Comment: due to the nature of the interventions (oral vs vaginal medication) blinding would have been difficult. Nonetheless this might have influenced (perception of) outcome.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no blinding of outcome assessment.

Nielsen 1999

Methods	Randomisation method not discussed in paper. Sahlgrenska University Hospital, Sweden. No information on study duration.
Participants	122 women < 13 weeks with symptoms of threatened miscarriage (bleeding +/- pain), a closed cervix, and ultrasound demonstration of pregnancy non-viability (anembryonic pregnancy n = 44; embryonic/fetal death n = 46; 'complex mass with deformed gestational sac' n = 32). Surgical evacuation at day 5 if transvaginal ultrasound showed retained products > 15 mm diameter.
Interventions	Mifepristone (400 mg orally) followed by oral misoprostol (400 mcg) 48 hours later (n = 60) vs expectant management (n = 62).
Outcomes	Clinical events; routine transvaginal ultrasound at 5 days to identify retained products; visual analogue scale to assess pain at day 5; visual analogue scale to assess satisfaction at day 14.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	Seeking clarification from authors if "complex mass with deformed gestational sac" represents missed or incomplete miscarriage. Data included in meantime.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: randomisation method not discussed in paper.
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment.
Incomplete outcome data (attrition bias)	Low risk	Comment: no loss to follow-up, no signs of missing data.

Nielsen 1999 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Comment: no signs of selective reporting.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: article does not state that in the expectant management group placebo were used. Therefore there probably was no blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessment, probably not done.

Niromanesh 2005*

Methods	Randomisation method not discussed in paper. Mirza Khochak khan Hospital, Tehran, Iran. No information on study duration.
Participants	100 women in Tehran, Iran, with fetal deaths between 14 and 25 weeks.
Interventions	Vaginal misoprostol: 400 mcg (n = 50) vs 600 mcg (n = 50) - both 12-hourly for 48 hours.
Outcomes	Miscarriage; surgical evacuation; adverse effects.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: randomisation method not discussed in paper.
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no information on loss to follow up, number of eligible patients, etcetera.
Selective reporting (reporting bias)	Unclear risk	Comment: side effects mentioned in the results (table 2) were not mentioned in the methods section; unclear if these were all outcomes that were measured.
Other bias	Low risk	No other source of bias could be detected

Niromanesh 2005* *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information on blinding, also no statements on use of placebo. Probaby no blinding (since the difference between 2 or 3 tablets would be clear for both patients as well as personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessment, probably not done.

Petersen 2013

Methods	This was a parallel group randomised controlled study performed between September 2005 and July 2010 at 2 hospitals in Australia. Randomisation was performed using a computer-generated model with a block size of 6 stratified for study site.
Participants	Inclusion criteria Clinically confirmed early pregnancy loss 6 + 0 and 12 + 6 weeks' gestation. Haemodynamically stable and not requiring emergency treatment. Willingness and consenting to undergo medical management. Ready access to emergency medical care (lives within 30 minutes of hospital). Immediate availability of another responsible adult with a driver's license. Ability to understand spoken English instructions without the need of a translator.
Interventions	Intervention: 400 mcg (n = 158) vaginal misoprostol; if needed repeated the next day vs 800 mcg (n = 152) vaginal misoprostol; if needed repeated the next day.
Outcomes	Outcomes: the primary outcome was the effectiveness to induce complete miscarriage, evaluated using 2 different methods. 1 Ultrasound criteria: complete = no gestational sac + an endometrial thickness < 30 mm on day 7 scan; incomplete = gestational sac or endometrial thickness > 30 mm3. 2 Clinical criteria: resolution of bleeding and pain, and return to a normal menstrual cycle, without the need for D&C at the completion of follow-up. Secondary outcomes included patient satisfaction and clinical outcomes – need for second dose; patient-reported side effects recorded in Study Questionnaire 1; adverse events; unplanned visits to a doctor or hospital Emergency Department; fall in haemoglobin from baseline.
Funding	Completion of this study was supported in part by a grant from the Toowoomba Hospital Foundation.
Declarations of interest	The authors have nothing to declare.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: randomisation was performed using a computer-generated model with a block size of 6 stratified for study site.

Petersen 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	Comment: allocation to the study groups was made by opening the next consecutively numbered, sealed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: data on incomplete follow-up are provided in figure 2 (participation flow chart).
Selective reporting (reporting bias)	Unclear risk	Comment: methods section states that adverse events were measured without further specification. It is unclear if the outcomes mentioned in table 3 were all that were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: the allocated dose was recorded in the medication chart and administered by the non blinded attending staff. The allocated dose was not revealed to the study population (although they would probably notice the difference between 2 or 4 tablets).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: the allocated dose was recorded in the medication chart and administered by the non-blinded attending staff. This attending staff seems to also have performed the ultrasounds after treatment.

Rita 2006

Methods	Parallel randomised controlled trial, permuted block method randomisation. This study was carried out in the department of obstetrics and gynaecology, SMGS Hospital, Government Medical College, Jammu, J&K in the year 2002-2003
Participants	A total of 100 women consented to participate in the study. The specified inclusion criteria were a period of gestation less than 13 weeks, haemodynamically stable women with haemoglobin more than 10gm%, closed cervical os, axillary temperature of less than 37.50 C, no previous history of inflammatory bowel disease or allergy to misoprostol.
Interventions	Intervention: 400 mcg of misoprostol was given orally and repeated every 4 hours for a maximum of 3 doses if required (n = 50). Control: 600 mcg of misoprostol was inserted in posterior vaginal fornix and the second dose was repeated after 4 hours (n = 50).
Outcomes	The primary outcome evaluated was drug-induced complete expulsion of the conceptus (within 10-12 hours). Secondary outcome evaluated were side effects, induction expulsion interval, number of doses required and permeability of cervical canal in those women who required surgical evacuation.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Rita 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation other than permuted block method, not mentioned.
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment is not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no mentioning of missing data.
Selective reporting (reporting bias)	Unclear risk	Comment: methods section states that side effects were measured, without further specification. It is unclear if the outcomes mentioned in the results section were all the outcomes that were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: due to the nature of the intervention (oral vs vaginal medication) blinding of participants and personnel would be very difficult.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: there is no description of an independent doctor assessing the outcome.

Saichua 2009

Methods	Parallel randomised controlled trial. Randomisation scheme was generated using a random number table. This RCT was performed at Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, from June 2007 to May 2008.
Participants	Pregnant women with·13 weeks of gestation who came to antenatal care clinic or gynaecologic outpatient department, diagnosed with embryonic death or anembryonic pregnancy by transvaginal ultrasound were recruited into the study. Embryonic death was defined as an intrauterine pregnancy with a fetal pole longer than 6 mm without cardiac activity. Anembryonic pregnancy was defined as an intrauterine gestational sac of diameter more than 20 mm without embryonic pole or yolk sac.
Interventions	Intervention: 600 mcg powdery sublingual misoprostol (n = 26). Control: 600 mcg sublingual misoprostol (n = 28).
Outcomes	The primary outcome measure was complete abortion. The secondary outcome measure was the duration of complete abortion and side effects.
Funding	No information on funding.
Declarations of interest	'Conflicts of interest statement: none.'
Notes	
Risk of bias	
Bias	**Authors' judgement** / **Support for judgement**

Saichua 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomization scheme was generated using a random number table. The co investigator generated the allocation sequence, and study staff enrolled participants and assigned participants to their groups. When a woman met the study inclusion criteria, the study staff picked a sequentially numbered opaque envelope which contained a ticket indicating treatment group".
Allocation concealment (selection bias)	Low risk	Quote: "The co investigator generated the allocation sequence, and study staff enrolled participants and assigned participants to their groups". Comment: study staff assigned patients to a group by picking a sequentially numbered opaque envelope. Adequate type of allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: according to the flowchart there were no patients lost to follow up, furthermore, there were no patients who discontinued the intervention.
Selective reporting (reporting bias)	High risk	Comment: the methods section states that a specific outcome (headache) was measured, however this was not reported in the results section.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Neither the provider nor the woman was blinded to the treatment regimens".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessment, considering the provider was not blinded also outcome assessment was probably not blinded.

Schreiber 2018

Methods	Parallel multi-centre randomised controlled trial
Participants	Women with an anembryonic pregnancy, embryonic or fetal death with a gestational age between five and 12 weeks
Interventions	200 mg of mifepristone, administered orally, followed by 800 mcg of misoprostol, administered vaginally (mifepristone-pretreatment group) or 800 mcg of misoprostol alone, administered vaginally (misoprostol-alone group)
Outcomes	Treatment success (defined as complete expulsion without the need of additional vacuum aspiration within 30 days after treatment) Secondary outcomes reported were rate of vacuum aspiration, blood transfusion, pelvic infection, side effects of medication such as nausea, diarrhoea, headache and fever.
Funding	Supported by the National Institute of Child Health and Human Development of the National Institutes of Health (Eunice Kennedy Shriver award number R01-HD0719-20 [to Dr. Schreiber] and Women's Reproductive Health Research award number K12-HD001265-18 [to Dr. Sonalkar]).
Declarations of interest	Dr. Creinin reports receiving consulting fees from Danco Laboratories. No other potential conflict of interest relevant to this article was reported.
Notes	

Schreiber 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned in permuted blocks of two to eight, stratified according to trial site, with the use of Research Electronic Data Capture software".
Allocation concealment (selection bias)	Low risk	Quote: "Participants were randomly assigned in permuted blocks of two to eight, stratified according to trial site, with the use of Research Electronic Data Capture software."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 women lost to follow-up in intervention arm, 1 in the control arm. For 2 women, reasons for lost to follow-up were not mentioned. In 1 women there was a suspicion of caesarean section scar pregnancy
Selective reporting (reporting bias)	High risk	Quote: "assessments of quality of life, costs, and biomarkers that predict complete gestational sac expulsion were performed, but the data are not presented here". It is not mentioned if these outcomes are or will be presented elsewhere.
Other bias	Low risk	No other bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no placebo was used, therefore blinding was not possible for both personnel and participants.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At the initial follow-up visit, an investigator who was unaware of the treatment-group assignments assessed the outcome by means of endovaginal ultrasonography.

Shah 2010*

Methods	This was a prospective randomised open-labelled trial conducted in the Department of Obstetrics and Gynaecology Unit-III at Civil Hospital Karachi. No information on study duration.
Participants	The inclusion criteria was an ultrasound diagnosis of missed miscarriage < 20 weeks' gestation.
Interventions	Intervention: (n = 25) 400 mcg of misoprostol sublingually every 3 hours for a maximum of 5 doses. Patients having a gestational age of more than 12 weeks whose uterine size was also more than 12 weeks were given 200 mcg of misoprostol instead of 400 mcg in both sublingual and vaginal groups. Control: (n = 25) 400 mcg of misoprostol vaginally every 3 hours for a maximum of 5 doses. Patients having a gestational age of more than 12 weeks whose uterine size was also more than 12 weeks were given 200 mcg of misoprostol instead of 400 mcg in both sublingual and vaginal groups.
Outcomes	The primary outcome measures were, complete evacuation of POC, mean induction to delivery time and the occurrence of side effects.
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	

Shah 2010* *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: article states the study was a randomised controlled trial, however there is no information on type of random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: allocation was concealed using sealed envelopes, though depending on the randomness, allocation might have been predictable.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcomes are presented for all 50 patients.
Selective reporting (reporting bias)	Unclear risk	Comment: there seems to be no loss to follow-up or incomplete data; outcomes were reported for all 50 patients. Table 3 shows 'side effects' without further specification, unclear which side effects were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: there is no information on blinding in the article. Due to the nature of the interventions (sublingual vs vaginal medication), blinding would be difficult.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: outcome seems not to be assessed by an independent doctor.

Sinha 2018

Methods	This study was a parallel double-blind RCT conducted at University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, from October 2011 to April 2013
Participants	Women with early pregnancy failure < 12 weeks of gestation.
Interventions	women were randomised to 200mg of oral mifepristone or placebo. 48 Hours later 800mcg of vaginal misoprostol and if necessary 400 mcg misoprostol were given orally at 3-hourly interval to a maximum of 2 doses in women < 9 weeks by scan and 4 doses in women > 9 weeks by scan similarly in both groups
Outcomes	Primary outcome was complete expulsion within 14 days after start treatment. Treatment success was defined as not needing any surgical intervention. Secondary outcomes were the need for surgical intervention due to heavy bleeding or incomplete expulsion by day 14. Other secondary outcomes were nausea/vomiting, bleeding and treatment acceptability.
Funding	no funding was mentioned
Declarations of interest	It was stated there were no conflicts of interest.
Notes	

Risk of bias

Sinha 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "sealed packets were numbered from 1 to 92 by simple randomization using computer generated random tables"
Allocation concealment (selection bias)	Low risk	Quote: "The third party used to dispense the coded sealed packet to the treating obstetrician".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there was one participant lost to follow-up in both groups.
Selective reporting (reporting bias)	Low risk	Comment: all pre-defined outcome measures were reported in the results section
Other bias	Low risk	No other bias could be detected.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: this was a placebo-controlled double-blind trial. The placebo consisted of tablets of 500 mg calcium who were similarly looking to the tablets of 200 mg mifepristone. Blinding seems adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: the outcome was assessed blinded since both caregiver and participant were blinded for the intervention.

Sonsanoh 2014

Methods	A prospective randomised trial was done to 120 healthy pregnant women with early pregnancy failure from August 2012 to August 2013, at the Department of Obstetrics and Gynecology, Chonburi Hospital, Thailand.
Participants	Women with early pregnancy failure, defined as 1) an intrauterine gestational sac with a mean diameter of 25 mm or greater and no visible embryonic pole; 2) an embryonic pole of 5 mm to14 mm with no cardiac activity; and 3) abnormal growth or persistent absence of fetal cardiac activity on a second scan 7-10 days later(16). In addition, all participants should be over 18 years old.
Interventions	In Group 1 (n = 60), they were given 4 tablets of 200 mcg misoprostol with 2-3 drops of normal saline placed in the posterior vaginal fornix by digital insertion. In Group 2 (n = 60), 4 tablets of 200 mcg misoprostol were sublingually given.
Outcomes	Complete abortion; defined as the termination of pregnancy with the complete expulsion of conceptus without the need for surgical intervention or additional misoprostol dose. If the complete abortion did not occur, the repeated induction in the same route would be done every 6 hours for maximum of 3 doses. The treatment was considered a failure if the pregnancy was still continuing after 48 hours from the third dose of misoprostol. Furthermore, adverse effects were measured.
Funding	No information on funding.
Declarations of interest	The authors do not have any conflict of interest.
Notes	
Risk of bias	

Sonsanoh 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "We used and assigned blocks of four randomizations to two groups of participants" Comment: This does not state how the randomisation list was created.
Allocation concealment (selection bias)	Low risk	Quote:"'Cards labelled with the assigned route were placed in sealed, opaque envelopes which were filled and labelled in accordance with the list of randomizations. The allocation was concealed by the use of sealed number of treatments".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: according to table 2 all 120 patients randomised completed the study. 19 patients did not have complete abortion, therefore in table 3 (time-to-delivery interval) only 50 and 51 patients in each group are described. This does make sense.
Selective reporting (reporting bias)	Low risk	Comment: there are no signs of selective outcome reporting. All outcomes mentioned in the methods section were presented in the results section.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: blinding is not described. Due to the nature of the intervention (vaginal vs sublingual medication) blinding would be difficult; nonetheless this might have influenced (perception of) outcome.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: the article does not state that outcome assessors were blinded.

Tang 2003

Methods	Randomisation by quote: "computer-generated random numbers". Queen Mary Hospital, Hong Kong SAR, China. No information on study duration.
Participants	80 women with non-viable pregnancies diagnosed by ultrasound < 13 weeks.
Interventions	Group 1: 600 mcg misoprostol sublingually every 3 hours for maximum of 3 doses (n = 40); group 2: 600 mcg misoprostol vaginally every 3 hours for maximum of 3 doses (n = 40). Women discharged home after completion of treatment and reassessed day 7 - when surgical evacuation performed if gestation sac still present, or retained POC plus heavy bleeding.
Outcomes	Primary outcome: complete miscarriage (defined as no need for surgical evacuation up until return of menstruation).
Funding	No information on funding.
Declarations of interest	No information on conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Tang 2003 *(Continued)*

Random sequence generation (selection bias)	Low risk	Comment: computer-generated random numbers.
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcomes were presented for all 80 patients that were initially randomised.
Selective reporting (reporting bias)	Unclear risk	Comment: table 3 shows several side effects. The methods section states only that 'side effects' were measured without further specification. It is unclear if other side effects than the ones presented in table 3 were also measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no blinding of participants and personnel. Sublingual misoprostol was taken by the patient itself while vaginal misoprostol was administered by a research nurse.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessment. Probably not done.

Tang 2006

Methods	Open parallel RCT. Eligible women were randomised according to computer-generated random numbers into 2 groups. The study was carried out from July, 2002 to January, 2004; Queen Mary Hospital, Hong Kong SAR, China.
Participants	Women with (i) intrauterine gestational sac with a mean sac diameter of ≥ 2 cm without a fetal pole; (ii) presence of a fetal pole with no cardiac pulsation; (iii) the gestational sac was < 2 cm with no interval growth or persistent absence of fetal cardiac pulsation on rescanning 7–10 days later.
Interventions	Women in both groups (total n = 180) received 600 mcg misoprostol sublingually every 3 hours for a maximum of 3 doses (day 1). Additionally, women in group 2 (n = 90) also received 400 mcg misoprostol sublingually daily for a further week (day 2–8).
Outcomes	The outcome of the study was assessed on day 9. A transvaginal ultrasound examination of the pelvis was performed The primary outcome measure was the complete miscarriage rate. The incidence of side effects, duration of vaginal bleeding and the change in haemoglobin level were also studied.
Funding	The work described in this paper was supported by a grant from the Committee on Research and Conference Grants of The University of Hong Kong of the Hong Kong Special Administrative Region, China.
Declarations of interest	No information on conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Tang 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Eligible women were randomized according to computer-generated random numbers into two groups".
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: according to the flowchart, there was no loss to follow up and no missing data.
Selective reporting (reporting bias)	Unclear risk	Comment: table 3 shows several side effects. The methods section only states that 'side effects' were measured without further specification. It is unclear if the effects mentioned in table 3 were the only side effects that were measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This was an open randomized study and both the subjects and the investigators knew the treatment that the women had received". Comment: due to the nature of the interventions blinding was practically impossible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: there is no information on blinding of outcome assessment available; it seems that outcome was not assessed by an independent doctor.

Tanha 2010a

Methods	Parallel randomised controlled trial. Randomisation using a computer-generated code. Recruitment took place at Mirza Kochak Khan Hospital, a premier research and referral facility, in Tehran, Iran, from January 2005 through to February 2007.
Participants	(i) intrauterine gestational sac with a mean sac diameter of < 2 cm without a fetal pole; (ii) presence of a fetal pole with no cardiac activity; and (iii) gestational sac < 2 cm with no interval growth or persistent absence of fetal cardiac pulsation on rescanning 7–10 days later. Additional eligibility criteria included having no known contraindications to misoprostol, general good health and no vaginal bleeding.
Interventions	Intervention: 400 mcg tablets every 6 hours sublingually (n = 110). Control: 400 mcg tablets every 6 hours vaginally (n = 110).
Outcomes	The primary outcome measure was efficacy of the treatment in inducing complete abortion, which was defined as passing of the POC without needing vacuum aspiration or dilatation or curettage; incomplete abortion as expulsion of the fetus but some POC remaining in the uterus, needing evacuation; and missed abortion as a gestational sac in the uterus without cardiac activity on ultrasound examination, needing emptying of the uterus. Success rate was defined as no need for surgical intervention. If a woman from either group did not bleed within 48 hours after completing the protocol, she was requested for a TVS scan. If a gestational sac was still found on TVS examination, surgical evacuation was performed. Other outcome measures were side effects recorded 1 hour up to 24 hours after every administration of misoprostol at the hospital by women after the treatment, until the first follow-up visit. Side effects were classified as pregnancy-related, treatment-related, and those related to the abortion process itself.
Funding	No information on funding.

Tanha 2010a *(Continued)*

Declarations of interest	This study is Dr Mohadeseh Feizi's postgraduate thesis.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: using a computer-generated code.
Allocation concealment (selection bias)	Unclear risk	Quote: "The study investigator opened the next sequentially numbered randomized envelope to determine the treatment arm. This randomization scheme was created by Population Council staff, using a computer-generated code". Comment: it is still unclear who put the randomisation scheme in the envelopes and if the envelopes were opaque.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all 220 patients were analysed.
Selective reporting (reporting bias)	Unclear risk	Comment: the methods section states that 'side effects' were measured without further specification, it is unclear if the side effects presented in the results are the only ones measured.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Neither the investigator nor the woman was blinded to the treatment assignment". Comment: due to the nature of intervention blinding would be practically impossible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: outcome was not assessed by independent doctors.

Trinder 2006

Methods	Randomised controlled trial comparing medical and expectant management with surgical management of first trimester miscarriage. This was a multi-centre trial with 7 participating hospitals, each of which had an early pregnancy clinic. Recruitment started in May 1997 and finished in December 2001.
Participants	Women with a pregnancy of less than 13 weeks' gestation who had been diagnosed as having either an incomplete miscarriage or early fetal/embryonic demise were eligible.
Interventions	Intervention: in the medical management arm, women with an incomplete miscarriage were admitted to hospital and given a single vaginal dose of 800 mcg misoprostol.1200 women with early fetal or embryonic demise were pre-treated with a single oral dose of 200 mg mifepristone,21 then admitted to hospital 24-48 hours later for a single vaginal dose of 800 mcg misoprostol (n = 398). Control: women in the expectant management arm were allowed home with no intervention (n = 399).

Trinder 2006 *(Continued)*

	Control: women in the surgical management arm were admitted for surgical suction curettage under general anaesthesia (n = 403).
Outcomes	Confirmed gynaecological infection at 14 days and 8 weeks; need for unplanned admission or surgical intervention.
Funding	The MIST study was funded by a South and West NHS Executive research and development grant. A donation of £20 000 was accepted from Exelgyn. Neither the NHS Executive nor Exelgyn had any role in the study design; collection, analysis, or interpretation of data; writing of the report; or the decision to submit the paper for publication.
Declarations of interest	The study group accepted a donation of £20 000 from Exelgyn, the manufacturers of mifepristone. The authors have no other competing interests.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was by a central telephone system at the Clinical Trials Services Unit, Oxford. We used minimisation to ensure comparability between women with respect to participating centre, parity, type of miscarriage, and gestation". Comment: this still does not state how the randomisation scheme was generated.
Allocation concealment (selection bias)	Low risk	Comment: use of a central telephone system for randomisation, operated by other persons than the doctors randomising the patients.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: according to the flowchart loss to follow-up was < 10%.
Selective reporting (reporting bias)	Low risk	Comment: flow chart displays all eligible and recruited women. No signs of selective reporting; all outcomes mentioned in the methods section were presented in the results section.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: there is no information on blinding of patients and personnel. However, due to the nature of the interventions, blinding would be practically impossible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information on blinding of outcome assessment, probably not done.

Wood 2002

Methods	Computer-generated random number list in blocks. Pharmacy prepared numbered envelopes. Tablets not identical so placed by nurse in opaque vaginal introducer for physician to insert - to maintain allocation concealment.

Wood 2002 *(Continued)*

	Department of Obstetrics and Gynecology, University of Calgary, Calgary, Alberta, Canada; between February 1999 and April 2000.
Participants	50 women with ultrasound diagnosed non-viable pregnancies. Gestational age 7-17 weeks but women not included if fetal size by ultrasound > 12 weeks equivalent. Also excluded from recruitment if experiencing uterine cramping or bleeding.
Interventions	Misoprostol (800 mcg vaginally) (n = 25) or vaginal placebo (n = 25). If complete miscarriage not suspected after 24 hours, treatment was repeated. At 48 hours, if no miscarriage or miscarriage thought to be incomplete, uterine curettage was offered.
Outcomes	Sample size based on reduction of uterine curettage from 50% to 10%. Women's satisfaction also assessed, but are not included in analyses as data not reported from control group.
Funding	This work was supported by a grant from the Office of the Associate Dean of Research, Faculty of Medicine, University of Calgary.
Declarations of interest	No information on conflicts of interest.
Notes	Analysis by intention-to-treat.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: computer-generated random number list in blocks.
Allocation concealment (selection bias)	Low risk	Comment: pharmacy prepared numbered envelopes. Tablets not identical so placed by nurse in opaque vaginal introducer for physician to insert - to maintain allocation concealment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: it seems that all patients completed the study. Outcomes were presented for all patients.
Selective reporting (reporting bias)	Low risk	Comment: no signs of selective reporting. Outcome measures mentioned in the methods section were presented in the results section.
Other bias	Low risk	No other source of bias could be detected
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: tablets not identical so placed by nurse in opaque vaginal introducer for physician to insert - to maintain allocation concealment. This assures blinding of patients and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: no information on blinding of outcome assessment. Considering that there was blinding of the physician treating the patient (by the use of a opaque vaginal introducer with either misoprostol or placebo) probably the physician was also blinded for outcome assessment.

AP diameter: anterior-posterior diameter
bHCG: beta human chorionic gonadotrophin
CRL: crown-rump length
ERPC: evacuation of retained products of conception
hCG: human chorionic gonadotropin
IM: intramuscular
IU: international units

IUFD: intrauterine fetal death
mcg: microgram
mm: millimetre
MTX: methotrexate
POC: products of conception
RCT: randomised controlled trial
TVS: transvaginal sonography
vs: versus
µL: microlitre

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbas 2018	Participants do not meet inclusion criteria (includes women undergoing termination of pregnancy for other reasons than non vital pregnancies, and up to a GA of 27 weeks).
Abd-El-Maeboud 2012	Termination of 'viable' pregnancies; the intervention is priming before medical treatment and not the treatment itself.
Abdel Fattah 1997	Conference abstract. No information about GA but, given title, probably includes pregnancies > 24 weeks as well as < 24 weeks.
Al-Bdour 2007	Quasi-randomised trial, patients assigned to treatment according to military ID number.
Ali 2018	Different topic, study includes women induced with balloon catheters and not with medication.
Almog 2005	Termination of 'viable' pregnancies - mainly with fetal anomalies.
Altaf 2006	Not a randomised study. No subgroup analysis with only patients with missed abortion and GA < 24 weeks.
Amjad 1999	Other subject; ‘priming’ of cervix while Foley catheter in situ.
Anderman 2000	Conference abstract. Includes pregnancies > 24 weeks as well as < 24 weeks.
Anderson 2009	Conference abstract. Duration of pregnancy unclear.
Ara 2009	Conference abstract.
Arellano 2009	Conference abstract on other subject. Treatment of incomplete abortion.
Avila-Vergara 1997	Intrauterine deaths mainly third trimester.
Aye 2017	Conference abstract, further results not published. It is not clear if also women with incomplete miscarriage were included in this study.
Azra 2007	Termination of pregnancies for congenital malformations as well as non-viable pregnancies. No subgroup analyses.
Bagratee 2009	Conference abstract on other subject. Predictive/etiologic study, size of RPOC as predictor of successful treatment.
Bani-Irshaid 2006	Other subject (TOP); no subgroup analysis of women with GA < 24 weeks.
Bartz 2013	Other subject, randomised trial of 2 methods for dilatation of the cervix before surgical evacuation.

Study	Reason for exclusion
Bebbington 2002	Termination of viable pregnancies.
Behrashi 2008	Includes patients with GA < 24 weeks and > 24 weeks; and patients with 'viable' pregnancies. No subgroup analyses performed. We tried to contact the authors by e-mail but they could not be reached.
Behrashi 2010	Not a publication of study results but a registration of a RCT in Iranian Trial Register.
Ben-Meir 2009	RCT comparing priming with misoprostol vs placebo before oxytocin induction. Patients with GA > 24 weeks included.
Betstadt 2007	Registration of trial protocol, no results published. Author was contacted, stated that the trial was stopped prematurely because of a lack of participants.
Bique 2007	Trial concerning treatment of incomplete abortion.
Biswas 2007	Termination of pregnancy because of various reasons, no subgroup analyses on patients with missed miscarriage or early fetal death. We tried to contact the authors but could not reach them.
Blohm 2005	Includes patients with incomplete (ongoing) miscarriage (with gestational residue between 15 mm to 50 mm).
Brouns 2010	Trial also includes patients with legal termination of viable pregnancies. We contacted the authors to ask for subgroup analyses of only patients with non-viable pregnancies; but the original data were not accessible to them anymore.
Cabrol 1990	Trial of mifepristone for induction of labour after intrauterine death - but mainly late second and third trimester pregnancies.
Caliskan 2005	Includes all patients with indication for termination of pregnancy; but does not state which indications are meant. We tried to contact the authors but could not reach them.
Caliskan 2009	Other subject (termination of pregnancy).
Chaudhuri 2015	Reference of trial registration. Results were published in 2015. Study participants included women with second and third trimester intrauterine fetal death. No subgroup analyses for GA < 24 weeks.
Chowdhury 2012	Conference abstract. No information on GA.
Clevin 2001	Abstract in Danish. A prospective, randomised study carried out to clarify the effect of vaginal administration of a prostaglandin E1 analogue (gemeprost) versus surgical management (curettage) on miscarriages at up to 12 weeks of gestation. 3 groups: 1 (n = 27), 2A (n = 17) and 2B (n = 17), allocated according the endometrial thickness. The measured outcomes were reduction of endometrial thickness, duration of vaginal bleeding and pain, reported in a non-suitable format for analysis.
Dabash 2009	Conference abstract, other subject (treatment of incomplete abortion).
Dao 2007	Other subject (treatment of incomplete abortion).
Das 2014	Other subject; treatment of incomplete miscarriage.
David 2003	Randomised trial (details of randomisation unclear) of 2 methods to soften the cervix before surgical evacuation for early non-viable pregnancies. No usable clinical data, given short timescale between treatment and surgery.
David 2005	Other subject (cervical priming before surgical evacuation).

Study	Reason for exclusion
Demirezen 2018	The participants in this study do not meet the inclusion criteria for this review (gestational age up to 28 weeks, and termination of both vital and non vital pregnancies). The intervention studied (induction with different type of balloon catheter) does not meet the inclusion criteria for this review.
Dickinson 1998	Trial included women with fetal malformations and maternal indications for pregnancy termination between 14 and 28 weeks, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Dickinson 2002	Trial included women with fetal malformations and maternal indications for pregnancy termination between 14 and 30 weeks, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Dickinson 2003	Randomised trial comparing oral with vaginal administration of misoprostol to terminate pregnancies with fetal malformations - not non-viable pregnancies.
Diop 2009	Other subject; treatment of incomplete abortion.
El Sokkary 2016	Unclear up to which GA patients were included and if there were subgroup analyses made for patients with GA eligible for this review. Furthermore, unclear what type of randomisation was used and therefore if this truly was a randomised controlled trial. We tried to contact the author but there was no response.
Elami-Suzin 2013	Trial included also patients with therapeutic abortion; no subgroup analysis on only missed miscarriage other than 1 remark in text (time until expulsion shorter than therapeutic abortion'; but that is not an outcome in our review). Furthermore, all women underwent curettage after medication, so it would be impossible to draw conclusions about the primary outcome in the review (complete evacuation) because it would be unclear whether the uterus was empty because of the medication or because of the curettage.
Elhassan 2008	Includes patients with GA up to 28 weeks. We e-mailed the authors to ask for a subgroup analysis of patients with GA < 24 weeks, but they did not respond.
Eppel 2005	Trial included women with fetal malformations and maternal indications for pregnancy termination between 14 and 23 weeks, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Eslamian 2007	Study group also includes patients with maternal medical disorders, TOP because of congenital malformations and PPROM. We contacted the authors: there were no subgroup analyses of only patients with fetal demise.
Fadalla 2004*	Women included in this trial had a GA 13-28 weeks, no subgroup analysis for GA < 24 weeks was available
Feldman 2003	Trial included women with fetal malformations and maternal indications for pregnancy termination between 14 and 23 weeks, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Fernlund 2018	Includes women with ongoing miscarriage (vaginal blood loss in combination with a sonographically diagnosed non vital first trimester pregnancy).
Fiala 2005	Other subject (pain medication in requested abortion for socio-economic reasons).
Ghorab 1998	Trial included women with fetal malformations for pregnancy termination, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.

Study	Reason for exclusion
Gonzalez 2001	Trial included women with fetal malformations and maternal indications for pregnancy termination between 14 and 23 weeks, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Grimes 2004	Trial included women with other reasons for pregnancy termination, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Gronland 2002	Not a randomised trial. 3-centre study of women with non-viable pregnancies comparing 3 treatment regimens: misoprostol, mifepristone + misoprostol, surgical evacuation - with treatment regimen changing at each hospital every 4 months.
Guix 2005	Trial includes patients seeking termination of pregnancy because of congenital malformations.
Halimi 2004	Trial includes patients with termination of pregnancy because of fetal demise or congenital malformations, up to GA of 28 weeks. No subgroup analyses available.
Hassan 2007	Quasi-randomised trial; other subject (treatment of incomplete abortion).
Hausler 1997	Prospective RCT evaluating 3 interventions for complete spontaneous abortion. Diagnosis was based on positive pregnant test, vaginal bleeding and/or evacuation of tissue from the vagina, a closed uterine orifice with only slight bleeding on admission and a possible clear sonographic pregnancy diagnosis in the history. Interventions: A) n = 15 curettage; B) n = 20 only controlled and; C) n = 15 additionally treated for 10 days with an oral hormone intake of 2 mg norethisterone acetate and 0.01 mg ethinyl oestradiol 3 x day. Randomisation by sealed unmarked envelopes. 63 patients were included in the study and allocated randomly to each group. 13 women (20.6%) were excluded from the study after randomisation: 10 did not report for the planned follow-up control, 1 did not report for curettage, in 1 the height of the endometrium was > 8 mm and in 1 an ectopic pregnancy was diagnosed 6 days after the randomisation. The study only presents outcomes, in a non-suitable format, regarding hCG clearing time and duration of the secondary haemorrhage from the day of randomisation.
Heard 2002	Conference abstract. Unclear what type of randomisation; 12 patients were assigned to group A and 21 to group B which seems odd in cases of 1:1 and even in case of 1:2 randomisation; no further information on methodology. No full article for this trial found.
Herabutya 1997a	Includes patients with all GA; no subgroup analyses of only patients with GA < 24 weeks; authors could not be reached for further clarification.
Herabutya 2005	RCT of misoprostol for terminating viable pregnancies.
Hidar 2001	Trial included women with fetal malformations and maternal indications for pregnancy termination between 13 and 29 weeks, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Hidar 2005	Trial includes patients with GA > 29 weeks and patients with TOP because of congenital anomalies or PPROM. We contacted the authors: there were no subgroup analysis available of only patients with intrauterine fetal death.
Hill 1991	Trial includes fetal deaths in both second and third trimesters.
Hinshaw 1993	Henshaw 1995: conference abstract. No subgroup analysis of randomised proportion (trial was partly randomised and partly treatment according to patients preference). Hinshaw 1993: interim results of partially randomised trial; no subgroup analysis on randomised patients, full results in other article. Hinshaw 1995: interim results of partially randomised trial; no subgroup analysis on randomised patients, full results in other article.

Study	Reason for exclusion
	Rispin 1993: conference abstract concerning study protocol of ongoing study; no results presented.
Hogg 2000	Abstract. Trial included women with other reasons for pregnancy termination, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Hombalegowda 2015	Conference abstract. No article with full results found. We tried to contact the authors to ask for such an article but could not reach them.
Hughes 1996	Cost-effectiveness analysis of previous study that included patients with incomplete miscarriage (no subgroup analysis on patients with fetal demise); partly randomised trial. We contacted authors for subgroup analysis on RCT patients with fetal demise, however they did not respond.
Imran 2010	Includes patients with GA > 24 weeks and TOP because of congenital malformations. We tried to contact the authors to ask for subgroup analyses but they did not respond.
Islam 2006	Not randomised; patients were divided in 2 equal groups. Trial included patients seeking TOP because of congenital malformations; no subgroup analysis on patients with fetal demise.
Jabir 2009a	Conference abstract. Other subject (cervical dilation before surgical evacuation).
Jabir 2009b	Conference abstract. Other subject (cervical preparation 3 hours before surgical evacuation).
Jain 1994	Trial included women with fetal malformations and maternal indications for pregnancy termination between 12 and 22 weeks, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Jain 1999	Trial included women with fetal malformations and maternal indications for pregnancy termination between 12 and 22 weeks, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Johnson 1997	RCT evaluating pain and bleeding and comparing surgical to medical treatment. Surgical arm (n = 12) uterine curettage under general anaesthesia. Medical arm (n = 17) include 3 different participant conditions and treatments: a) no treatment if women had a complete abortion and uterine cavity echo (myometrium) less than 15 mm; b) women with incomplete abortion: 1 mg pessary of gemeprost (Cervagem, May and Baker) and remained in hospital for 4 hours or until they had passed POC; and c) women with intact gestational sac (but non-viable fetus) 200 mg RU 486 (mifepristone) and then allowed home, readmitted 36-48 hours later for 1 mg of vaginal Cervagem. Data from each subgroup in the medical arm are not separated. The sample size is too small to detect any difference among such number of groups.
Kamal 2005	Quasi-experimental study, no RCT. Includes patients with GA > 24 weeks and with TOP because of maternal or fetal reasons.
Kanhai 1989	Includes both second and third trimester fetal deaths.
Kapp 2007	Quasi-randomised trial; trial includes patients seeking termination of pregnancy, indication for termination unclear.
Khosravi 2017	Trial registration, includes women with termination of first trimester pregnancies for early fetal demise as well as termination on maternal indication.
Kong 2013	Trial includes also patients with incomplete miscarriage. There is 1 sentence in results section that provides success rates for only patients with silent miscarriage ("Focussing on women who were diagnosed to have silent miscarriage at recruitment, complete miscarriage rate after surgical treatment, medical evacuation and expectant management was 97.7%, 63% and 62.5%, respectively"); but when these percentages are used to calculate the number of patients with successful treatment using the number of study participants in each group (49 surgical, 46 medical and 25 expectant management; see table 1) the outcomes are impossible. So it looks like either the percent-

Study	Reason for exclusion
	ages are not right, or not all patients with missed miscarriage were analyses. Unfortunately for this group there was no specific information on missing data.
Kurshid 2010	Trial includes patients wit indication for TOP because of IUFD, congential malformations, PPROM. We tried to contact the authors for subgroup analyses on only patients with IUFD, but could not reach them.
Kyaw 2015	Conference abstract. No information on method of randomisation. Authors could not be reached for further clarification.
Linn 2015	Conference abstract. Trial includes patients with GA > 24 weeks; no subgroup analysis of only patients with GA < 24 weeks available.
Lippert 1978	Second and third trimester fetal deaths. Not obviously randomised.
Lu 2014	Article in Chinese, after translation signs of weak methodology: no exact description of dosages of medication. Furthermore no information on type of randomisation.
Lughmani 2008	Conference abstract. Unclear if time span between treatment is too short (looks like surgical evacuation is performed within 12 hours after misoprostol treatment). Authors could not be reached for further clarification.
Machtinger 2004	Abstract. Appears to include both non-viable pregnancies and miscarriages.
Mahjabeen, 2009	Quasi-randomised trial. Includes patients with therapeutic TOP, unclear what indication for this TOP was.
Makenzius 2017	Trial that compares miscarriage care by midwife to care by physician; other topic.
Makhlouf 2003	Not clear from paper if all pregnancies complicated by fetal death. Seeking clarification from authors.
Martin 1965	Allocation based on alternation, not randomisation. Alternation violated.
Montesinos 2011	Wrong patient population ‘incomplete abortion’.
Moran 2005	Other topic (treatment of pregnancy of unknown location).
Mostafa-Gharebaghi 2010	Trial includes patients with termination of pregnancy because of fetal death, congenital malformations, PPROM and 'other causes'. We tried to contact the authors for subgroup analyses on only patients with fetal death, but could not reach them.
Mulayim 2009	Other subject (misoprostol after surgical treatment for miscarriage).
Naghshineh 2015	Trial included women with spontaneous miscarriage (non-viable pregnancy) < 17 weeks as well as induced abortion. No subgroup analyses for spontaneous miscarriage only.
Nakintu 2001	Both second and third trimester fetal deaths. Seeking separate data from author.
Nasreen 2009	Conference abstract. Trial includes patients with incomplete miscarriage.
Nassar 2006	Reference is trial registration. Trial was ended prematurely because of difficulties in recruitment of patients.
NCT02141555	Reference of trial registration. According to the trial register the current recruitment status is unknown, last updated in 2014. We did not find any published results.

Study	Reason for exclusion
NCT02573051	Reference of trial registration. According to the trial register the current recruitment status is unknown, last update in October 2015. We could not find any published results.
Ng 2015	Wrong patient population-'incomplete abortion'.
Ngai 2001	Includes data on women with both non-viable pregnancies and incomplete miscarriages. If these data can be separated by the researchers, these data may be included in the future.
Nguyen 2005	Other subject; treatment of incomplete abortion.
Niinimaki 2006	Trial also includes patients with incomplete miscarriage. We contacted the authors to ask for subgroup analyses on only patients with missed miscarriage and anembryonic gestation, however they did not respond.
Nor 2006	Other subject (termination of pregnancy; indication unclear), trial includes patients up to GA of 26 weeks; no subgroup analysis on patients with GA < 24 weeks.
Nuthalapaty 2005	Includes patients with induction because of congential malformations or maternal indications. 1 of the outcome measures was live birth rate (?). We tried to contact the authors for further clarification but could not reach them.
Nuutila 1997	Trial included women with fetal malformations and maternal indications for pregnancy termination between 12 and 24 weeks, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Owen 1999	Trial included women with fetal malformations and maternal indications for pregnancy termination between 16 and 24 weeks, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Paraskevaides 1992	Small study of 16 women "randomised" to surgical evacuation or prostaglandin F2alpha or Trilostane treatment. No details about clinical presentation or ultrasound and clinical findings, but from abstract includes both women with non-viable pregnancies and incomplete miscarriage.
Paritakul 2010	Wrong patient population-'incomplete abortion'.
Patua 2013	Other subject, treatment of incomplete miscarriage.
Perry 1999	Excluded women with fetal deaths.
Piotrowski 1979	Not clear that this was a randomised trial.
Pongsatha 2004	Trial excluded women with fetal deaths.
Prasartsakulchai 2004	Quasi-randomised: patients could choose for medical, surgical or expectant management. Only patients who chose medical management were further randomised. However patients did not meet inclusion criteria for the review, as they already experienced abdominal pain and vaginal bleeding, e.g. ongoing miscarriage, which is beyond the scope of this review.
Promwangkwa 2017	Participants in this study had a gestational age 14-24 weeks. Indications for termination of pregnancy included intra uterine fetal demise, but also termination of pregnancy of live fetus for other fetal and maternal indications. No subgroup analyses were made for IUFD up to 20 weeks of gestation.
Rahimi-Sharbaf 2015	Trial studies women with termination of pregnancy with GA 13-24 weeks because of congenital of maternal indications. No subgroup analyses were performed for only women with IUFD.

Study	Reason for exclusion
Ramadan 2009	Conference abstract. Other subject, incomplete abortion.
Ramsey 2004	Trial included women with other reasons for pregnancy termination, as well as pregnancies with fetal death. We tried to contact the authors but could not reach them.
Reeves 2006	Other subject (endometrial thickness as predictor for further intervention); no subgroup analyses on only patients with missed abortion.
Reeves 2008	Other subject (endometrial thickness as predictor for further intervention); no subgroup analyses on only patients with missed abortion.
Rivero-Lopez 1998	Other subject; cervical priming before intervention.
Robledo 2007	Other subject; predictive study (to identify indicators for success of misoprostol treatment).
Roy 2003	Abstract. Not clear if fetal death included as indication for termination.
Ruangchainikhom 2006	Other subject (termination of pregnancy because of obstetric reasons). Full data unavailable.
Saeed 2018	This trial meets all inclusion criteria. However data extraction was not possible. The table presenting the main results contained numbers of unknown origin. It was unclear whether percentages or number of participants were displayed. The numbers in this table did also not correspond with the main text, attributing to further doubt as to what the numbers in the table represent.
Salamalekis 1990	Abstract only. Treatment allocation by alternation, not by randomisation.
Salari 2012	Conference abstract. Other subject (other patient population); therapeutic abortion.
Shaheen 2017	In this trial women were not adequately randomised. The paper describes a quasi randomised trial with women being "divided into two groups".
Shaikh 2008	Conference abstract. No subgroup analysis on missed miscarriage.
Shelley 2005	Other subject; treatment of incomplete or ongoing miscarriage.
Shobeira 2007	Conference abstract. No article with full study results found. Authors could not be reached to ask for such an article.
Shochet 2012	Other subject (incomplete abortion).
Shokry 2009	Other subject, other intervention (reduction of bleeding after surgical evacuation).
Shuaib 2013	The type of randomisation is unclear. It seems that both groups had different types of follow up, especially for the surgically treated group it is unclear if they really all had successful outcome (for example: no information on ultrasound follow-up). Weak methodology, high risk of bias on all fronts.
Shwekerela 2007	Other subject (reduction of bleeding after surgical evacuation).
Smith 2006a	This was a qualitative study. No numeric comparison between the groups. Furthermore, study group includes women with an incomplete miscarriage; no subgroup analyses were performed for only patients with missed miscarriage.
Smith 2009	Study includes also patients with incomplete miscarriage. There was no subgroup analysis available for only patients with a non-viable pregnancy.

Study	Reason for exclusion
Srikhao 2005	Since patients participating in this study already experienced vaginal blood loss and abdominal pain this is considered ongoing or incomplete miscarriage; therefore this study is not eligible for the review.
Sripramote 2000	Other subject; cervical priming before surgical evacuation.
Stockheim 2006	The data presented in this trial were reciprocal. It is not valid to present reciprocal data for outcomes from trials because they are not reported in the way we have specified the review. This study was therefore not included in this review.
Su 2005	Termination of pregnancy for fetal anomalies, social reasons or maternal disease; not for non-viable pregnancies.
Suchonwanit 1999	Abstract of residents research paper. No article with full study results found; author could not be reached to ask for such an article.
Surita 1997	Abstract only. May include third trimester fetal deaths.
Tam 2005	Study investigating reproductive outcome after miscarriage treatment; patients were included in a previous trial. This previous trial was not retrieved from the search, but was identified screening the reference list of an excluded study; this trial also included patients with incomplete miscarriage. There were no subgroup analyses available for only patients with a non-viable pregnancy.
Tanha 2013	Unclear whether all patients meet inclusion criteria for review, it seems like also patients with legal abortion or TOP because of congenital malformations were included. We tried to contact the authors for further clarification but could not reach them.
Taylor 2011	Other subject; treatment of incomplete abortion.
Thavarasah 1986	Unclear from paper but allocation may have been by alternation. We tried to contact the authors but could not reach them.
Thida 2015	Conference abstract. We searched for full study results but could not find them. We tried to contact the authors to ask if there is an article with study results published, but could not reach them.
Toppozada 1994	Includes third trimester fetal deaths.
Toptas 2011	Conference abstract. No subgroup analysis of only patients with termination because of IUFD. Authors could no be reached for further clarification.
Torre 2012	Trial also includes patients with incomplete miscarriage. We tried to contact the authors for subgroup analysis on patients with missed miscarriage, but they did not respond.
Van Mensel 2009	Trial includes patients with GA > 24 weeks. We tried to contact the authors to ask for subgroup analyses on patients with GA < 24 weeks; but they did not respond.
Yapar 1996	Includes indications for termination other than fetal death. High degree of protocol violation (60/400). Results not presented as intention-to-treat.
Yilmaz 2005	Other subject; termination of pregnancy because of congenital or chromosomal abnormalities.
Yilmaz 2007	Other subject; termination of pregnancy because of congenital/chromosomal abnormalities.
Zanganeh 2012	Other subject; termination of pregnancy because of fetal or maternal problems.

Study	Reason for exclusion
Zhang 2000	Seems to be a trial about cervical priming before delivery. Outcome measures irrelevant for this review.
Zhang 2005	Includes both non-viable pregnancies and miscarriages. We tried to contact the authors to retrieve data on non-viable pregnancies only, but we could not reach them.

GA: gestational age
hCG: human chorionic gonadotropin
IUFD: intrauterine fetal death
mg: milligram
mm: millimetre
POC: products of conception
PPROM: preterm premature rupture of membranes
RCT: randomised controlled trial
RPOC: retained products of conception
TOP: termination of pregnancy

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12615000483550

Trial name or title	Buccal versus vaginal (200 microgram) misoprostol for second trimester abortion termination
Methods	Clinical randomised trial to compare efficacy and safety of vaginal and buccal misoprostol in second trimester abortion due to intrauterine fetal death
Participants	1. Women who are pregnant between 13 and 27 weeks. 2. Termination of pregnancy is indicated due to intrauterine fetal death
Interventions	The study had 2 treatment groups: group I received a dose of misoprostol (200 µg) (1 tablet of Misotac 200 µg; Sigma co., Cairo, Egypt) every 4 hours buccally (and the patient was instructed not to swallow it for 1 hour) till expulsion of the fetus for maximum 24 hours. Group II received a dose of moistened misoprostol (200 µg) (1 tablet of Misotac 200 ug; Sigma co., Cairo, Egypt) every 4 hours vaginally (tablet was put into the posterior fornix) till expulsion of the fetus for maximum 24 hours.
Outcomes	The primary outcome measure is the induction interval, the time from the initial misoprostol dose until complete fetal expulsion. Incidence of side effects of misoprostol (such as nausea, vomiting, fever, chills, diarrhoea, tachycardia, and headache) Number of misoprostol doses
Starting date	17/07/2012
Contact information	Dr Mohammad Sayed Abdellah; msayed21@yahoo.com
Notes	Last patient should have been included in 2013. It seems that the results have not been published (yet); no publications by the mentioned authors regarding this randomised controlled trial were retrieved in our extensive search.

Ali 2017

Trial name or title	Vaginal misoprostol in management of first trimester missed abortion
Methods	Randomised, parallel assignment, open-label trial
Participants	Inclusion criteria 1. Single dead fetus up-to 12 weeks 2. No low lying placenta 3. No scarred uterus 4. No or mild bleeding 5. No evidence of infection 6. Accepting to participate in the study
Interventions	Vaginal misoprostol (800 µg x 2 doses 3 hours) versus buccal/sublingual misoprostol (200 µg x 6 doses 4 hours)
Outcomes	Not specified
Starting date	Not yet recruiting
Contact information	Dr Mohammed Khairy Ali, Assiut University
Notes	

El Shahawy 2016

Trial name or title	Sublingual versus vaginal misoprostol in medical treatment of first trimestric missed miscarriage
Methods	Single-blind, randomised, parallel-assignment trial
Participants	Inclusion criteria 1. All women above 18 years of age 2. Less than 12 weeks of gestation 3. Pregnancy is confirmed by pregnancy test or ultrasound scan 4. Missed abortion 5. Normal general and gynaecological examination 6. The size of the uterus on pelvic examination was compatible with the estimated duration of pregnancy
Interventions	Sublingual misoprostol versus vaginal misoprostol
Outcomes	Primary outcome: completeness of abortion (expulsion of products of conception by visual inspection
Starting date	January 2016
Contact information	Ahmed Abdel Shafy El Shahawy, Ains Sham University
Notes	

NCT02620904

Trial name or title	Mifepristone induction for fetal demise, a randomised control trial
Methods	Double-blinded, randomised controlled trial with 1:1 allocation of mifepristone or placebo at initiation of induction of labour for fetal demise 20 weeks estimated gestational age or greater.
Participants	Inclusion criteria 1. Intrauterine fetal death as confirmed by absence of cardiac motion on ultrasound by attending physician at the time of admission to the hospital. 2. Estimated gestational age greater than 20 weeks 3. Haemodynamically stable and appropriate for induction of labour as per primary clinical health team in house 4. Women with 1 prior low transverse caesarean delivery
Interventions	Interventional arm: ingest 200 mg tablet of mifepristone orally. Control arm: ingest a placebo tablet orally with similar physical properties.
Outcomes	Time to delivery of fetus [time frame: from the initiation of medical therapy for induction to delivery of fetus]
Starting date	February 2016
Contact information	Montefiore medical centre, principal investigator: Jessica Atrio, MD, jatrio@montefiore.org
Notes	

NCT02633761

Trial name or title	Mifepristone and misoprostol versus misoprostol alone for treatment of fetal death at 14-28 weeks of pregnancy: a randomised, placebo-controlled double-blinded trial
Methods	Allocation: randomised Intervention model: parallel assignment Masking: quadruple (participant, care provider, investigator, outcomes assessor) Primary purpose: treatment
Participants	Inclusion criteria 1. Demised fetus of between 14 to 28 weeks duration confirmed by ultrasound 2. Have no contraindications to study procedure, according to provider 3. Be able to consent to procedure, either by reading consent document or by having consent document read to her 4. Be willing to follow study procedures
Interventions	Active comparator group 1: 200 mg mifepristone followed in 24 hours by repeated doses of 200 µg: buccal misoprostol given every 3 hours Placebo comparator group 2: placebo followed in 24 hours by 200 µg: buccal misoprostol given every 3 hours.
Outcomes	Complete uterine evacuation of the fetus and placenta without surgical intervention [time frame: 48 hours]

NCT02633761 *(Continued)*	
	Complete uterine evacuation of fetus and placenta using study drug alone without recourse to any additional surgical intervention
Starting date	April 2015
Contact information	Hillary Bracken, PhD; hbracken@gynuity.org
Notes	

NCT03212352 2017	
Trial name or title	Comparing two medical treatments for early pregnancy failure
Methods	Double-blind placebo-controlled randomised trial - parallel group assignment
Participants	Women with ultrasonographically confirmed early pregnancy failure (6-14 weeks postmenstrual), managed expectantly for at least 1 week
Interventions	Oral mifepristone (600 mg) or oral placebo
Outcomes	Primary outcome: complete evacuation 6 weeks after initial treatment (whether or not complete evacuation (total endometrial thickness < 15 mm) will be assessed through ultrasonography
Starting date	June 27 2018, estimated primary completion date = January 1 2020
Contact information	Charlotte C Hamel l.hamel@cwz.nl 0031243658750 Marcus P Snijders m.snijders@cwz.nl 0031243658750 Radboud University, The Netherlands Collaborators: Innovatiefonds Zorgverzekeraars, Canisius-Wilhelmina Hospital
Notes	

mg: milligram
mm: millimetre
µg: microgram

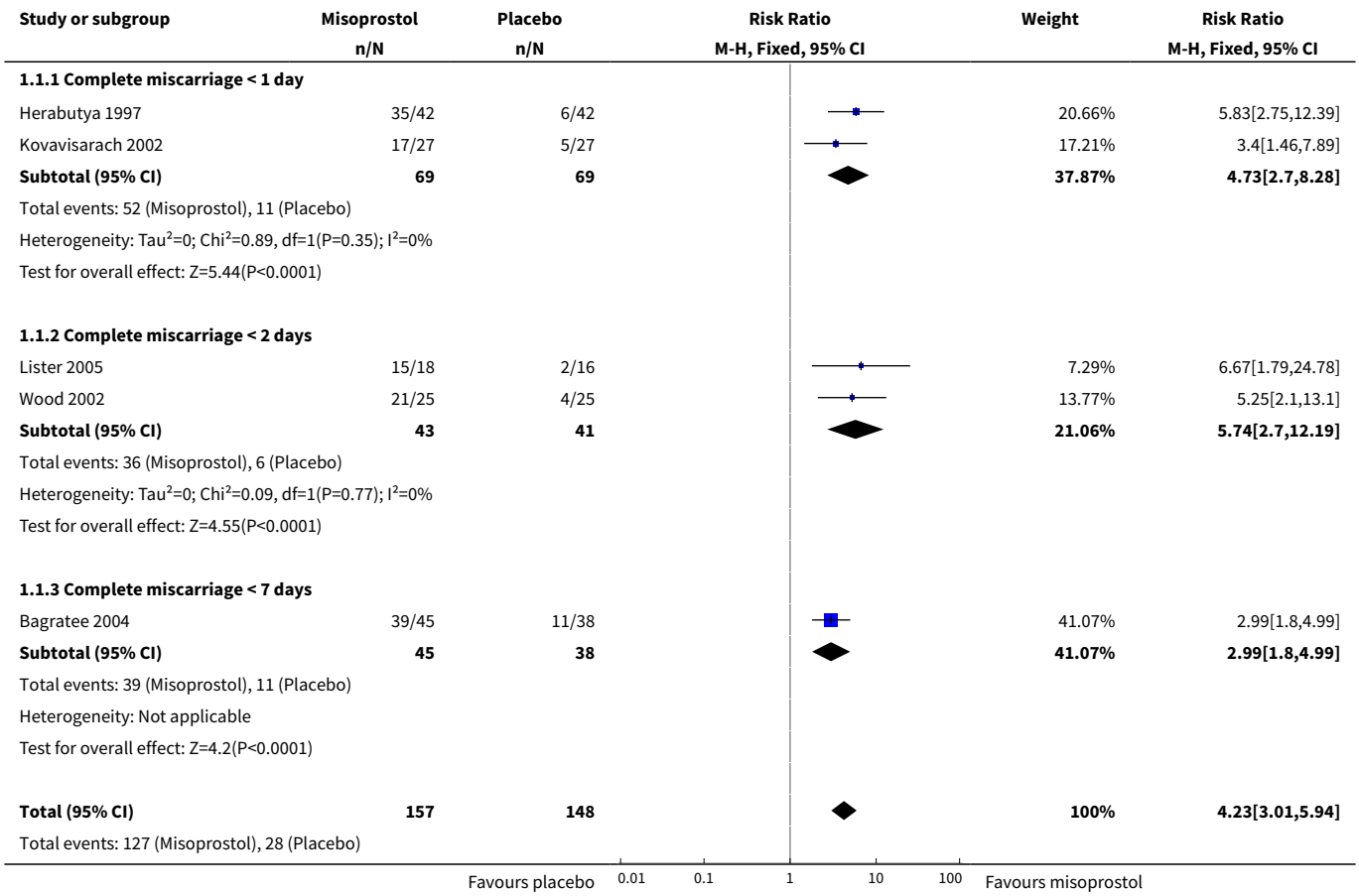
DATA AND ANALYSES

Comparison 1. Vaginal misoprostol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	5	305	Risk Ratio (M-H, Fixed, 95% CI)	4.23 [3.01, 5.94]
1.1 Complete miscarriage < 1 day	2	138	Risk Ratio (M-H, Fixed, 95% CI)	4.73 [2.70, 8.28]
1.2 Complete miscarriage < 2 days	2	84	Risk Ratio (M-H, Fixed, 95% CI)	5.74 [2.70, 12.19]
1.3 Complete miscarriage < 7 days	1	83	Risk Ratio (M-H, Fixed, 95% CI)	2.99 [1.80, 4.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Death or serious complications: uterine perforation	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.96]
3 Blood transfusion	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.04]
4 Blood loss: haemoglobin difference > 10 g/L	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.38, 4.12]
5 Days of bleeding: vaginal bleeding 2 weeks after treatment	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.41, 2.45]
6 Nausea	2	88	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.43, 4.40]
7 Diarrhoea	2	88	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [0.35, 14.06]
8 Pain (opiate use)	1	84	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 101.11]
9 Woman's satisfaction with treatment	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.83, 1.64]

Analysis 1.1. Comparison 1 Vaginal misoprostol versus placebo, Outcome 1 Complete miscarriage.



Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=3.39, df=4(P=0.49); I²=0%					
Test for overall effect: Z=8.31(P<0.0001)					
Test for subgroup differences: Chi²=2.46, df=1 (P=0.29), I²=18.66%					

Favours placebo 0.01 0.1 1 10 100 Favours misoprostol

Analysis 1.2. Comparison 1 Vaginal misoprostol versus placebo, Outcome 2 Death or serious complications: uterine perforation.

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Herabutya 1997	0/42	1/42		100%	0.33[0.01,7.96]
Total (95% CI)	**42**	**42**		**100%**	**0.33[0.01,7.96]**
Total events: 0 (Misoprostol), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					

Favours misoprostol 0.01 0.1 1 10 100 Favours placebo

Analysis 1.3. Comparison 1 Vaginal misoprostol versus placebo, Outcome 3 Blood transfusion.

Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Herabutya 1997	0/42	2/42		100%	0.2[0.01,4.04]
Total (95% CI)	**42**	**42**		**100%**	**0.2[0.01,4.04]**
Total events: 0 (Misoprostol), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					

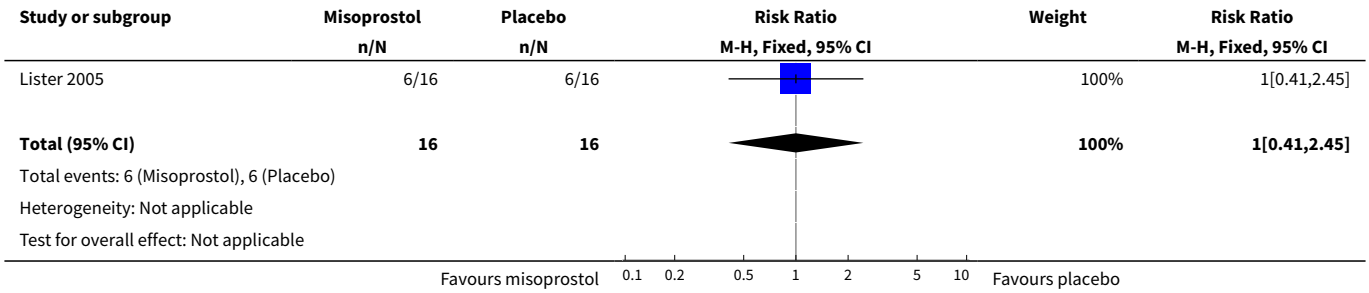
Favours misoprostol 0.001 0.1 1 10 1000 Favours placebo

Analysis 1.4. Comparison 1 Vaginal misoprostol versus placebo, Outcome 4 Blood loss: haemoglobin difference > 10 g/L.

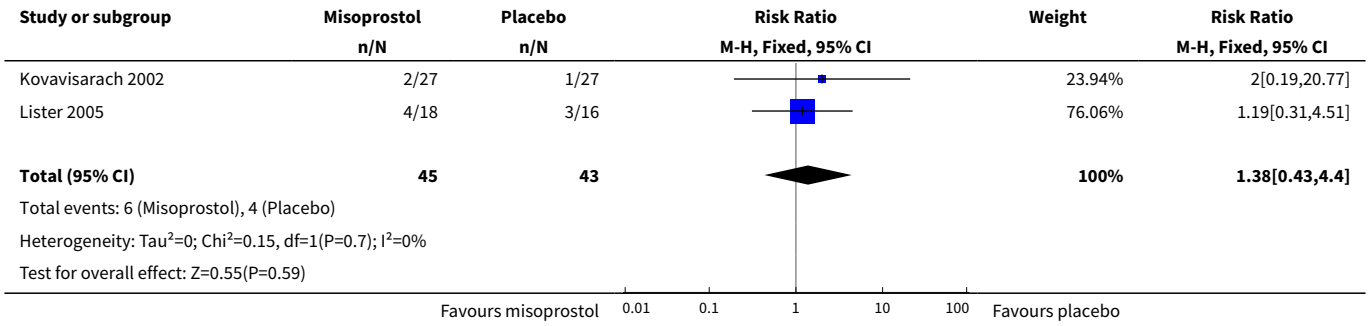
Study or subgroup	Misoprostol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Wood 2002	5/25	4/25		100%	1.25[0.38,4.12]
Total (95% CI)	**25**	**25**		**100%**	**1.25[0.38,4.12]**
Total events: 5 (Misoprostol), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					

Favours misoprostol 0.1 0.2 0.5 1 2 5 10 Favours placebo

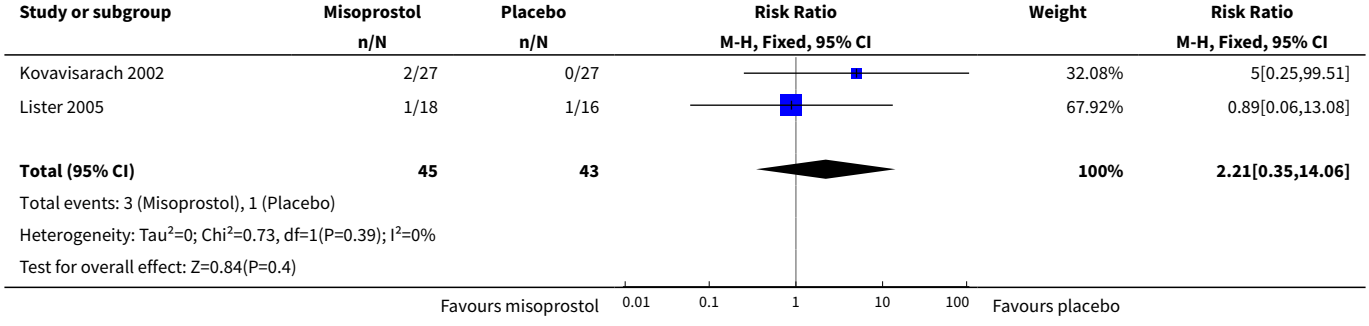
Analysis 1.5. Comparison 1 Vaginal misoprostol versus placebo, Outcome 5 Days of bleeding: vaginal bleeding 2 weeks after treatment.



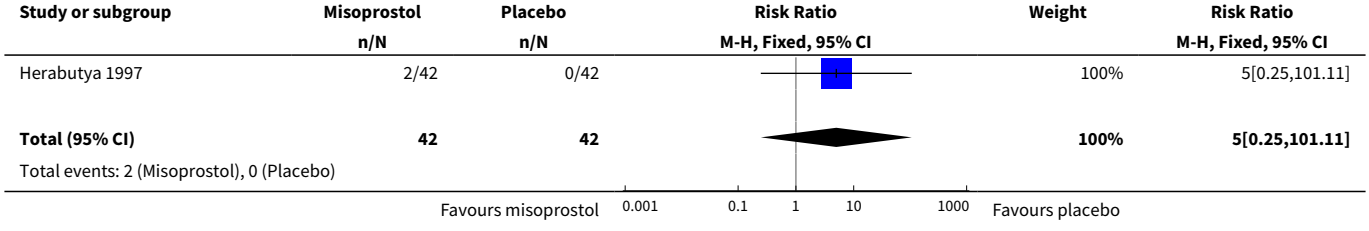
Analysis 1.6. Comparison 1 Vaginal misoprostol versus placebo, Outcome 6 Nausea.

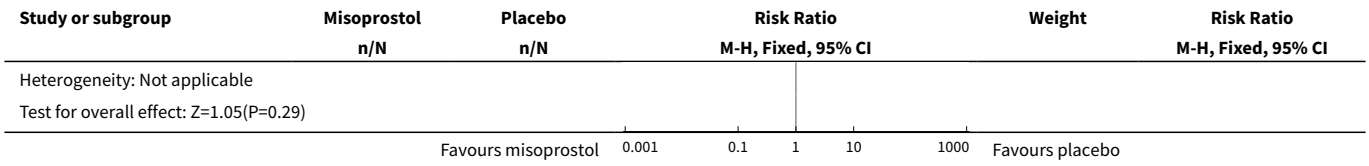


Analysis 1.7. Comparison 1 Vaginal misoprostol versus placebo, Outcome 7 Diarrhoea.

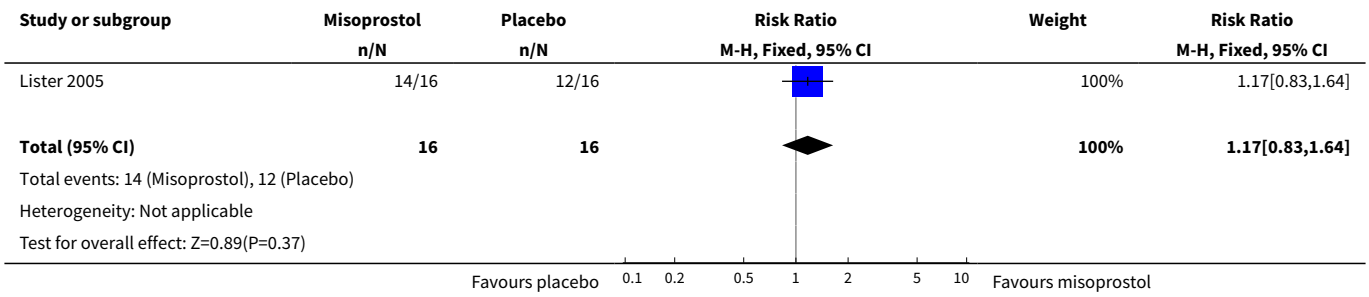


Analysis 1.8. Comparison 1 Vaginal misoprostol versus placebo, Outcome 8 Pain (opiate use).





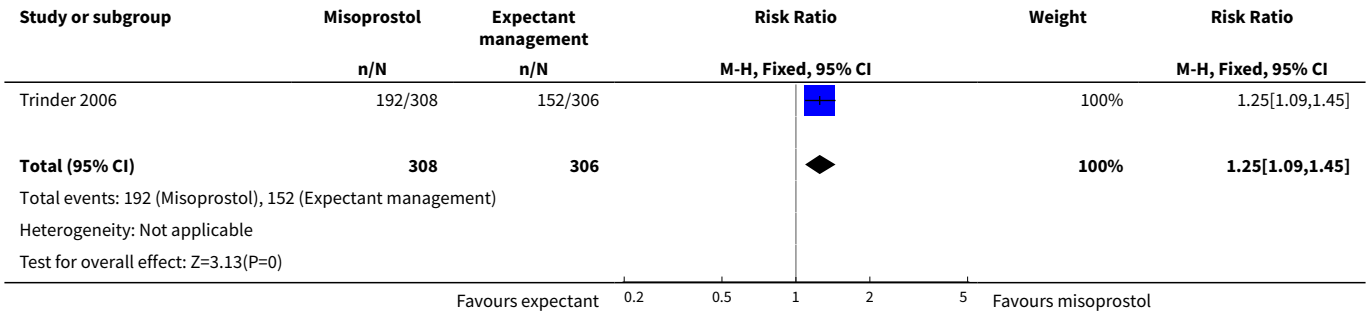
Analysis 1.9. Comparison 1 Vaginal misoprostol versus placebo, Outcome 9 Woman's satisfaction with treatment.



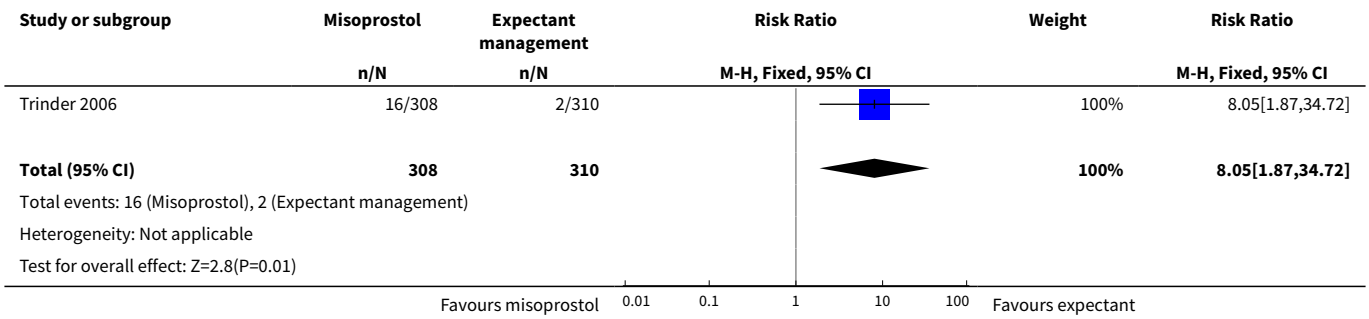
Comparison 2. Vaginal misoprostol versus expectant management

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	1	614	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.09, 1.45]
2 Pelvic infection	1	618	Risk Ratio (M-H, Fixed, 95% CI)	8.05 [1.87, 34.72]

Analysis 2.1. Comparison 2 Vaginal misoprostol versus expectant management, Outcome 1 Complete miscarriage.



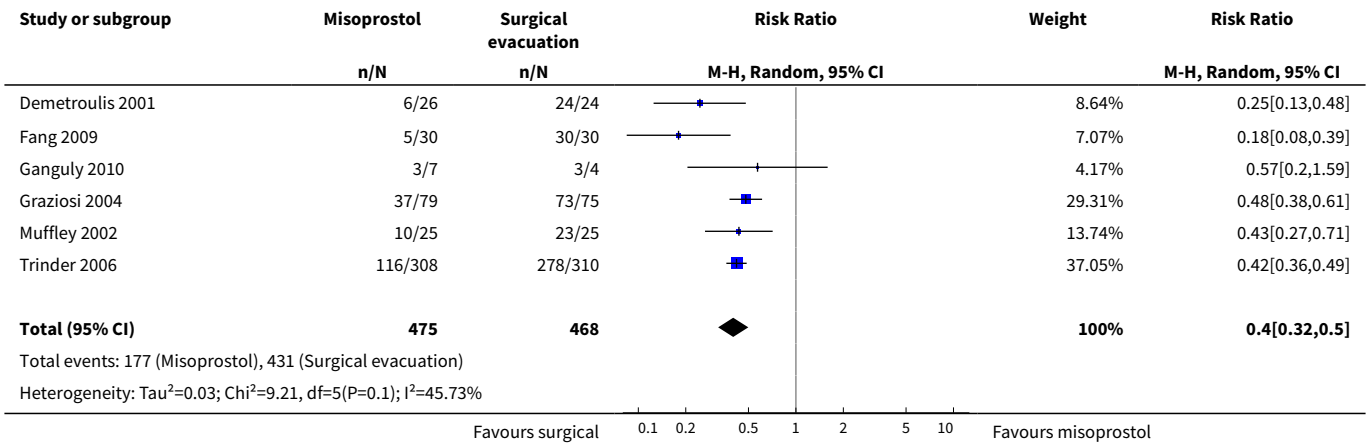
Analysis 2.2. Comparison 2 Vaginal misoprostol versus expectant management, Outcome 2 Pelvic infection.

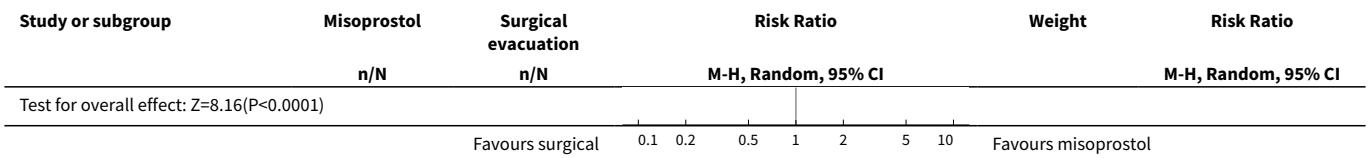


Comparison 3. Vaginal misoprostol versus surgical evacuation of uterus

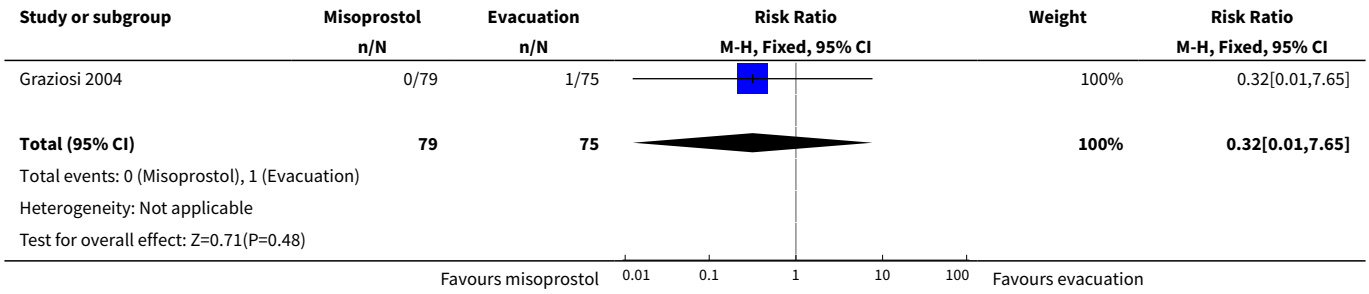
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	6	943	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.32, 0.50]
2 Uterine perforation	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.65]
3 Blood loss: post-treatment haematocrit (%)	1	50	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-3.51, 0.71]
4 Pain relief	1	154	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.82, 2.46]
5 Pelvic infection	1	618	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.39, 1.37]
6 Nausea	1	154	Risk Ratio (M-H, Fixed, 95% CI)	21.85 [1.31, 364.37]
7 Diarrhoea	1	154	Risk Ratio (M-H, Fixed, 95% CI)	40.85 [2.52, 662.57]
8 Woman's satisfaction	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.40, 1.11]

Analysis 3.1. Comparison 3 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 1 Complete miscarriage.

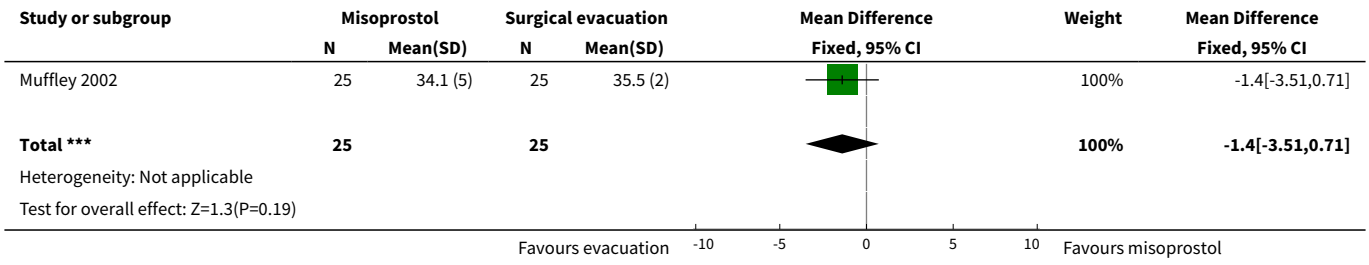




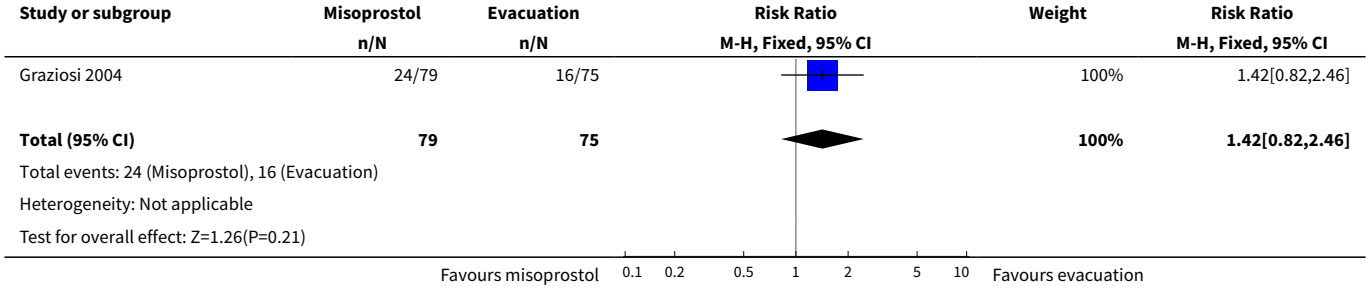
Analysis 3.2. Comparison 3 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 2 Uterine perforation.



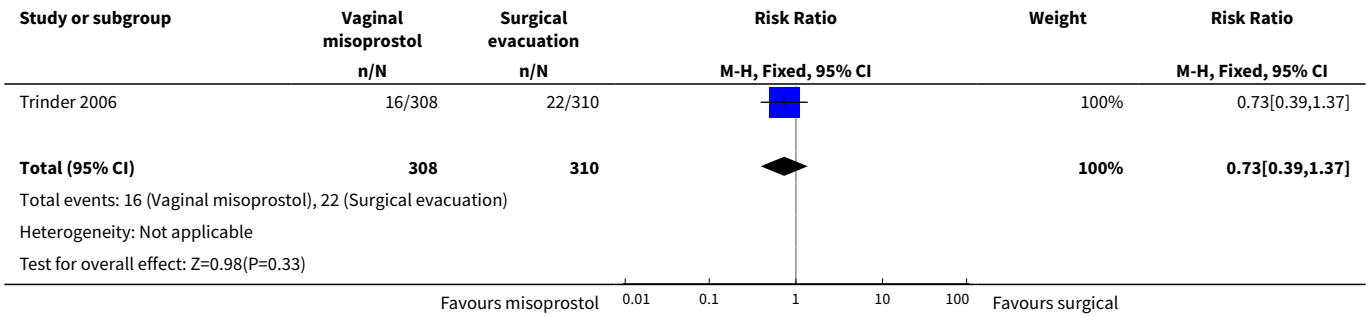
Analysis 3.3. Comparison 3 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 3 Blood loss: post-treatment haematocrit (%).



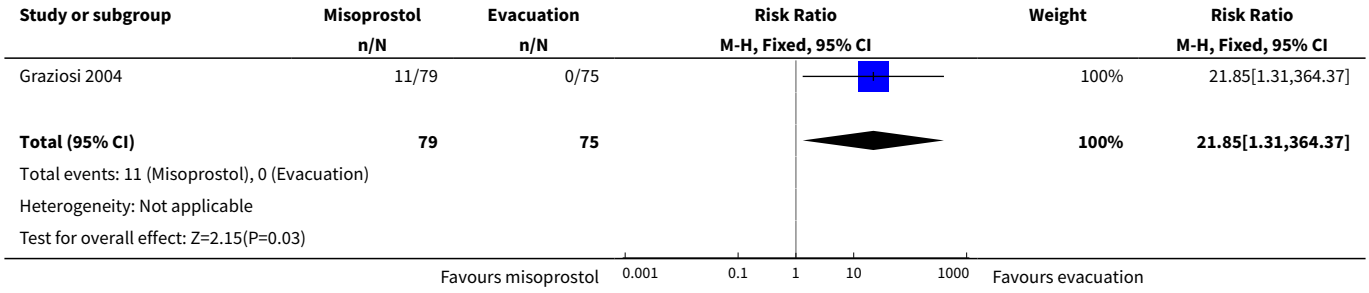
Analysis 3.4. Comparison 3 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 4 Pain relief.



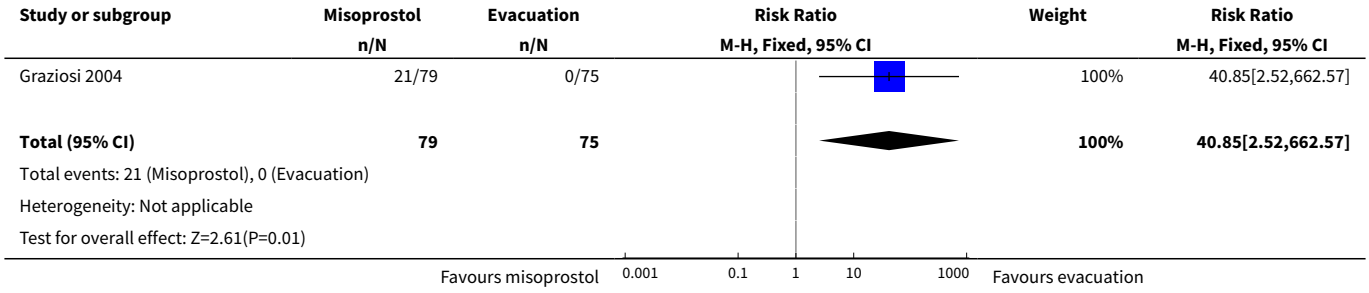
Analysis 3.5. Comparison 3 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 5 Pelvic infection.



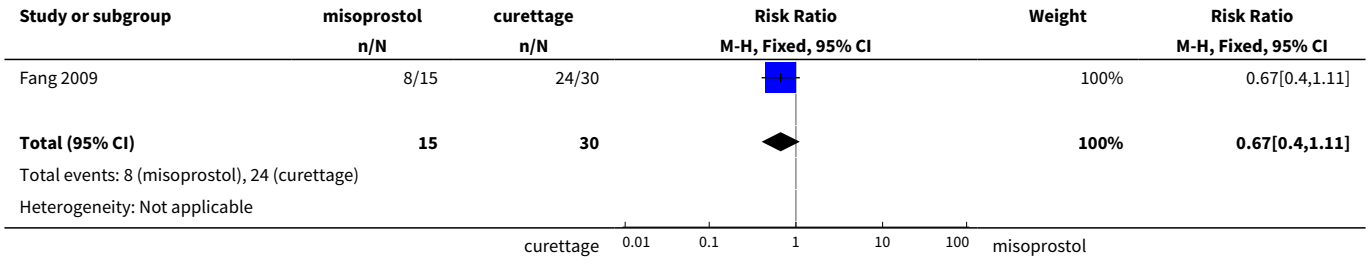
Analysis 3.6. Comparison 3 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 6 Nausea.

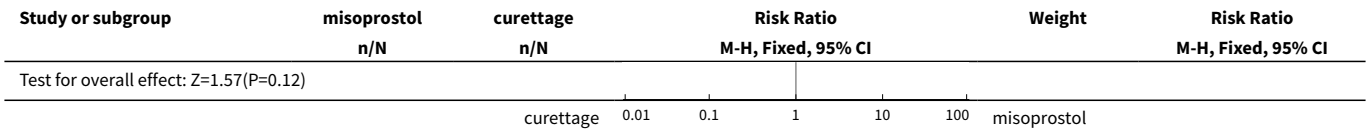


Analysis 3.7. Comparison 3 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 7 Diarrhoea.



Analysis 3.8. Comparison 3 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 8 Woman's satisfaction.

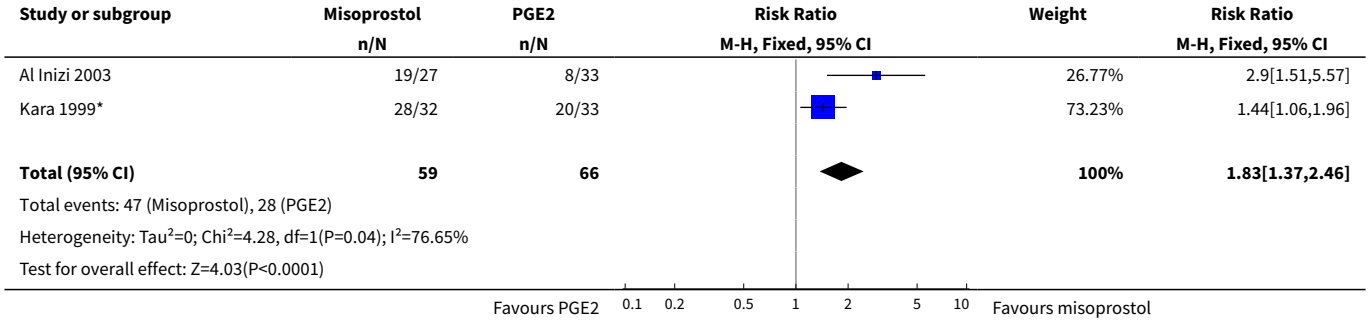




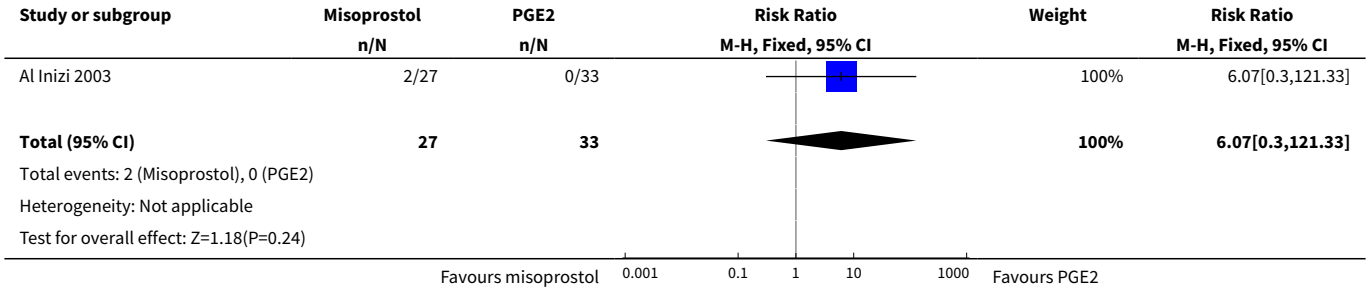
Comparison 4. Vaginal misoprostol versus vaginal dinoprostone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	2	125	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.37, 2.46]
2 Blood transfusion	1	60	Risk Ratio (M-H, Fixed, 95% CI)	6.07 [0.30, 121.33]
3 Nausea	1	65	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.28, 3.78]
4 Duration of hospital stay (days)	1	60	Mean Difference (IV, Fixed, 95% CI)	-2.38 [-3.36, -1.40]

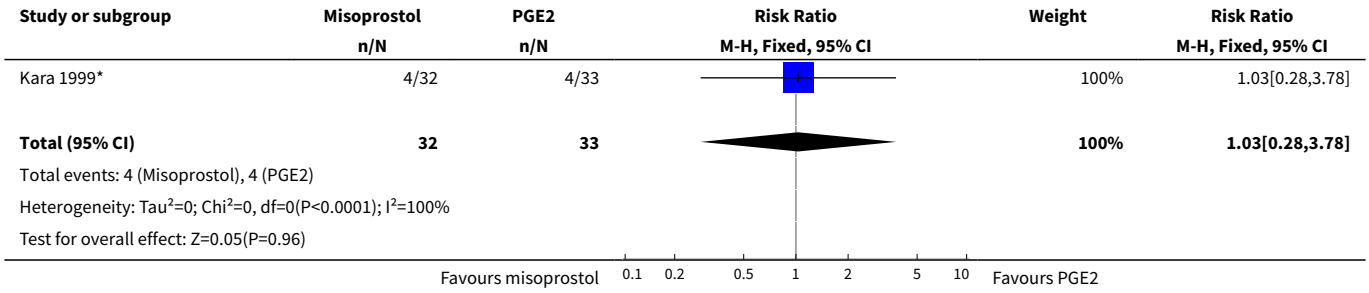
Analysis 4.1. Comparison 4 Vaginal misoprostol versus vaginal dinoprostone, Outcome 1 Complete miscarriage.



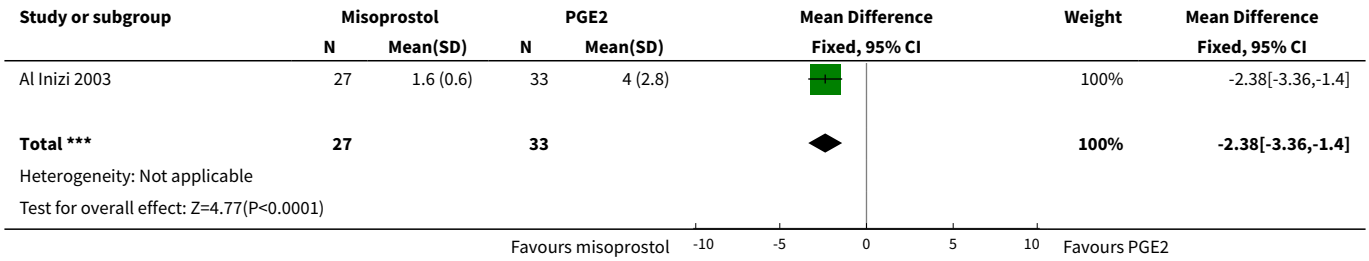
Analysis 4.2. Comparison 4 Vaginal misoprostol versus vaginal dinoprostone, Outcome 2 Blood transfusion.



Analysis 4.3. Comparison 4 Vaginal misoprostol versus vaginal dinoprostone, Outcome 3 Nausea.



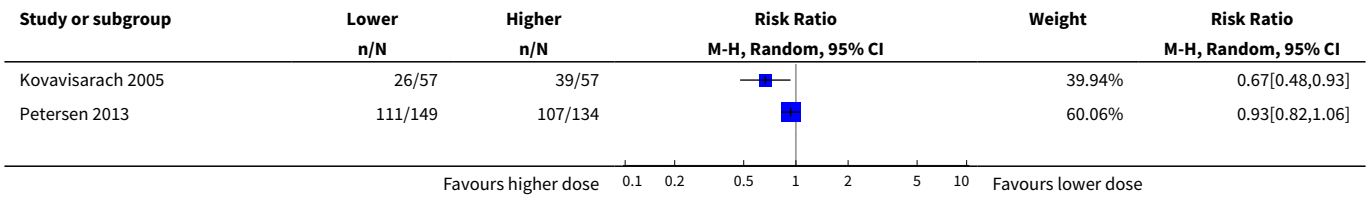
Analysis 4.4. Comparison 4 Vaginal misoprostol versus vaginal dinoprostone, Outcome 4 Duration of hospital stay (days).

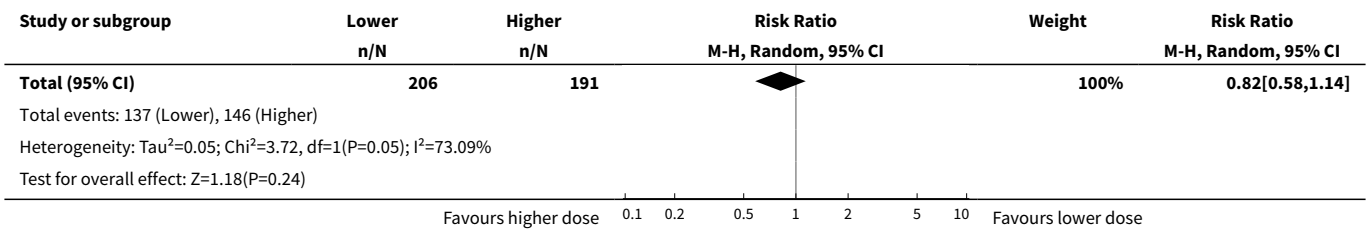


Comparison 5. Vaginal misoprostol lower versus higher-dose regimens

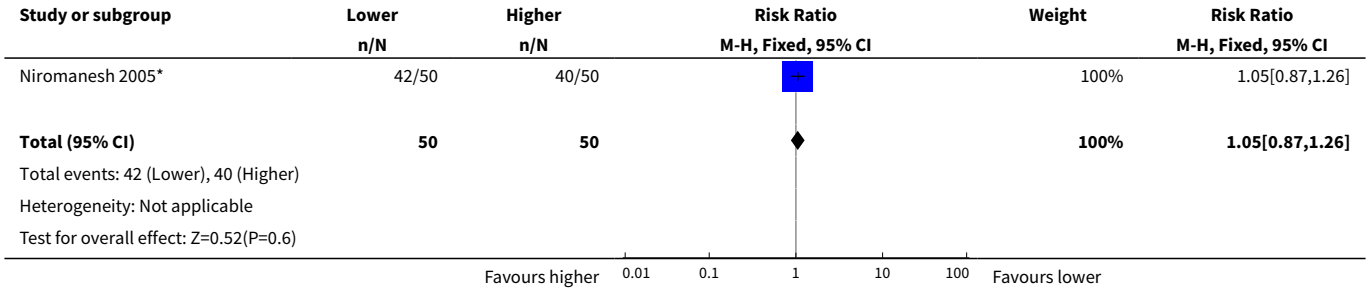
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage < 13 weeks	2	397	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.58, 1.14]
2 Complete miscarriage 13-23 weeks	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.87, 1.26]
3 Nausea	2	214	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.31, 1.41]
4 Diarrhoea	2	214	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.15, 1.91]

Analysis 5.1. Comparison 5 Vaginal misoprostol lower versus higher-dose regimens, Outcome 1 Complete miscarriage < 13 weeks.

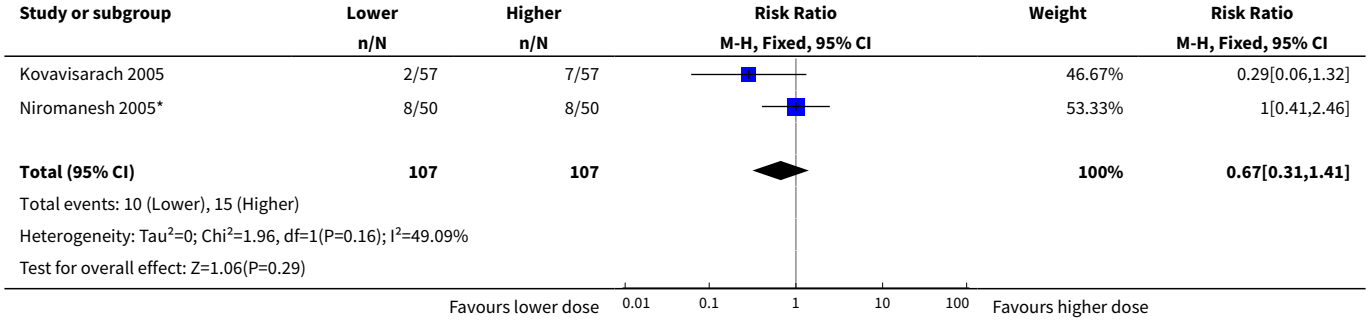




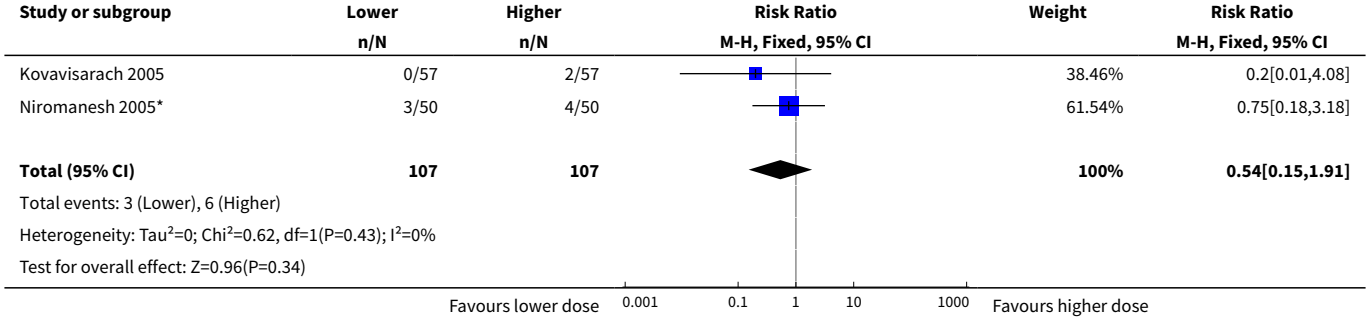
Analysis 5.2. Comparison 5 Vaginal misoprostol lower versus higher-dose regimens, Outcome 2 Complete miscarriage 13-23 weeks.



Analysis 5.3. Comparison 5 Vaginal misoprostol lower versus higher-dose regimens, Outcome 3 Nausea.



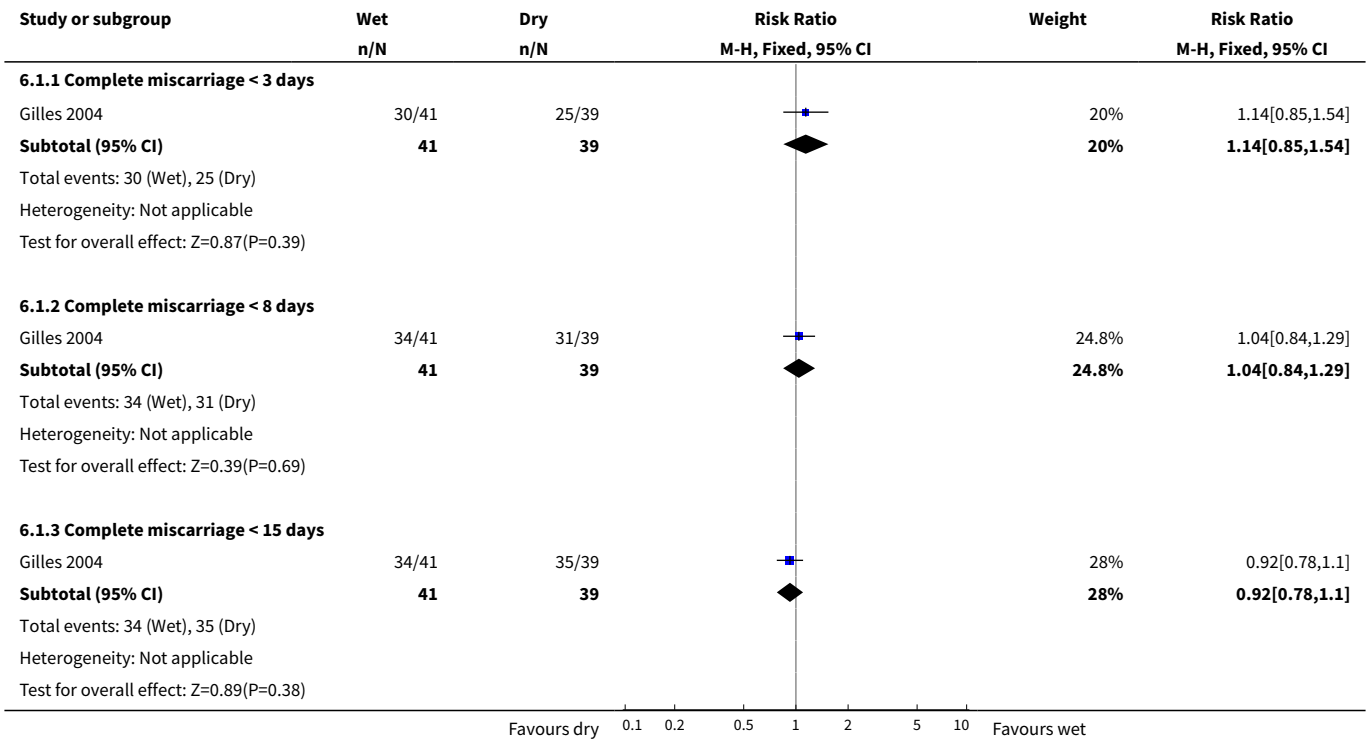
Analysis 5.4. Comparison 5 Vaginal misoprostol lower versus higher-dose regimens, Outcome 4 Diarrhoea.

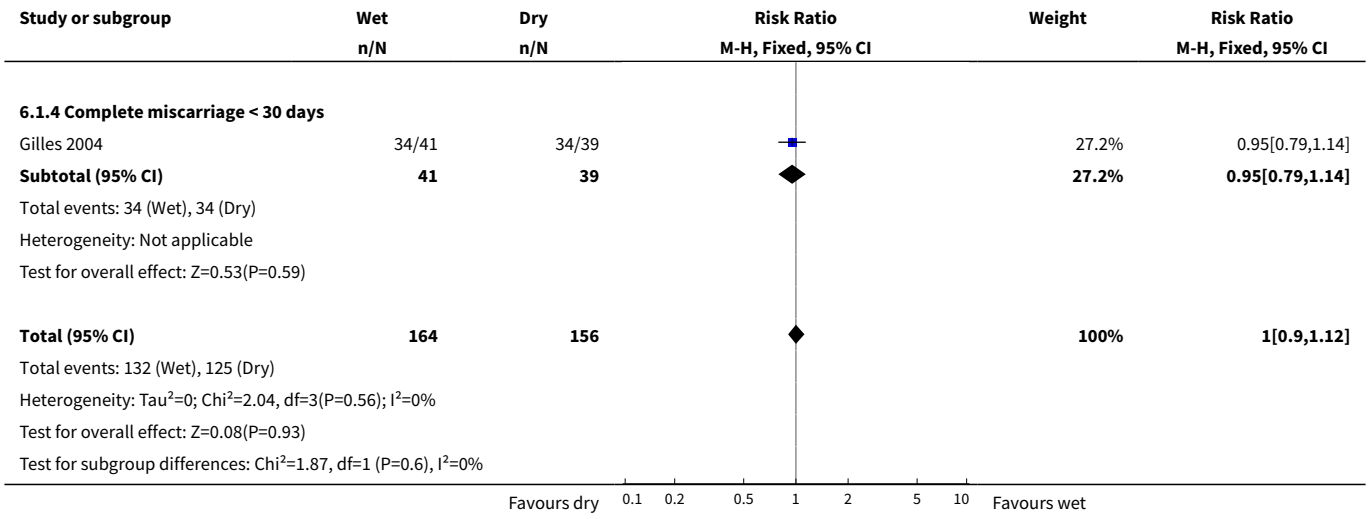


Comparison 6. Vaginal misoprostol wet versus dry vaginal preparations

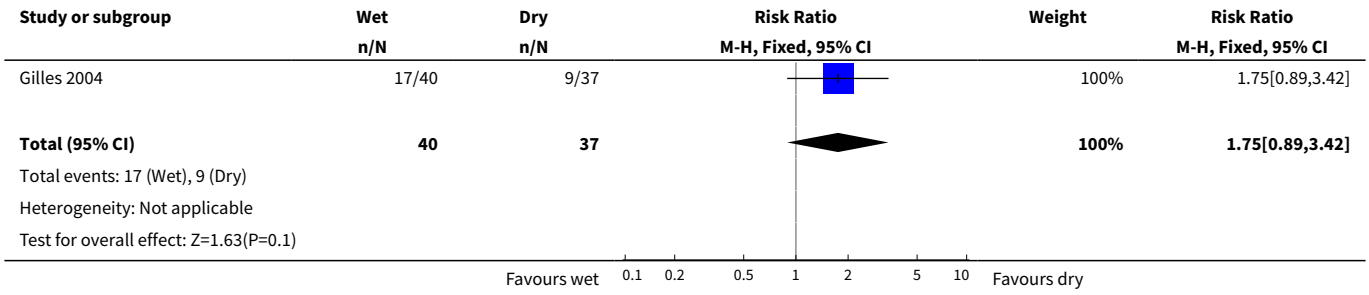
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	1	320	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.90, 1.12]
1.1 Complete miscarriage < 3 days	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.85, 1.54]
1.2 Complete miscarriage < 8 days	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.29]
1.3 Complete miscarriage < 15 days	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.78, 1.10]
1.4 Complete miscarriage < 30 days	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.79, 1.14]
2 Diarrhoea	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.89, 3.42]
3 Vomiting	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.33, 2.62]
4 Acceptability of method: would wish/probably wish same treatment in future nonviable pregnancy	1	73	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.93, 1.49]

Analysis 6.1. Comparison 6 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 1 Complete miscarriage.

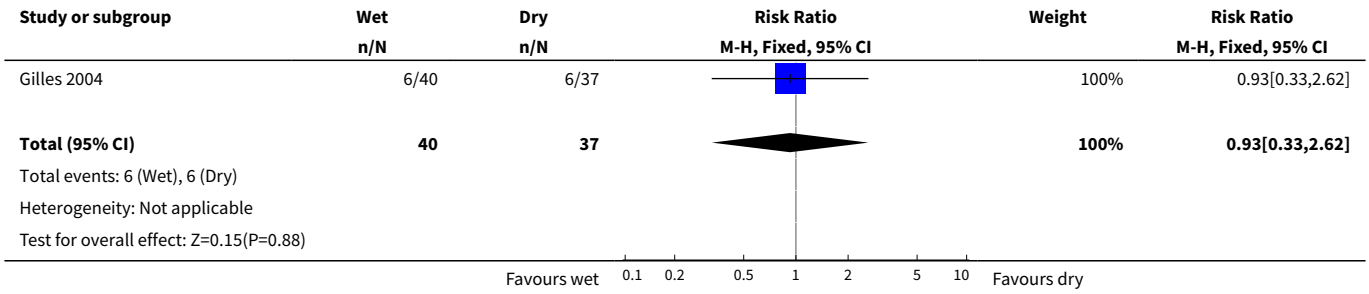




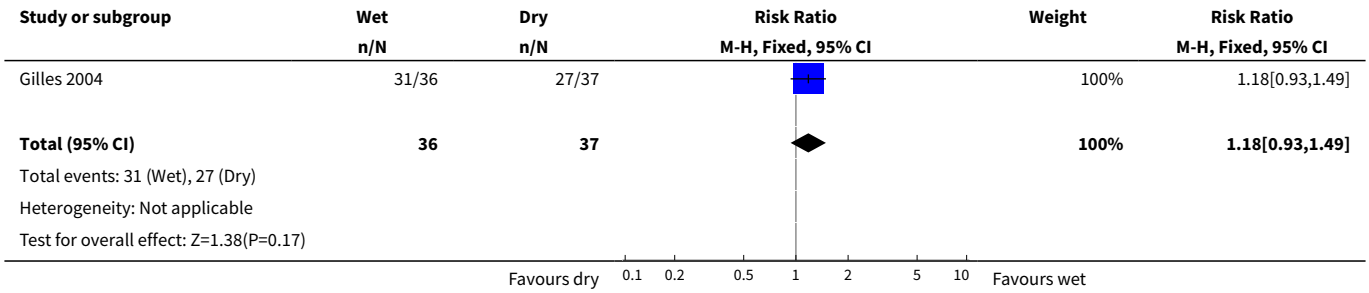
Analysis 6.2. Comparison 6 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 2 Diarrhoea.



Analysis 6.3. Comparison 6 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 3 Vomiting.



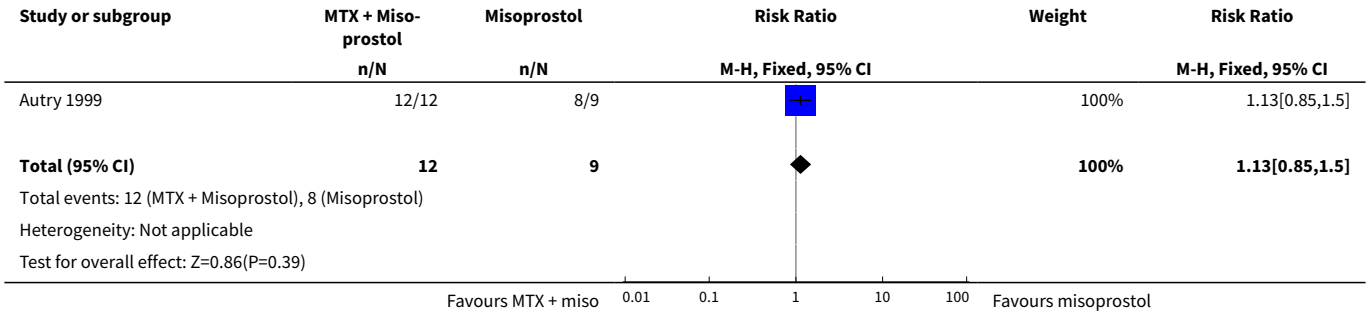
Analysis 6.4. Comparison 6 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 4 Acceptability of method: would wish/probably wish same treatment in future nonviable pregnancy.



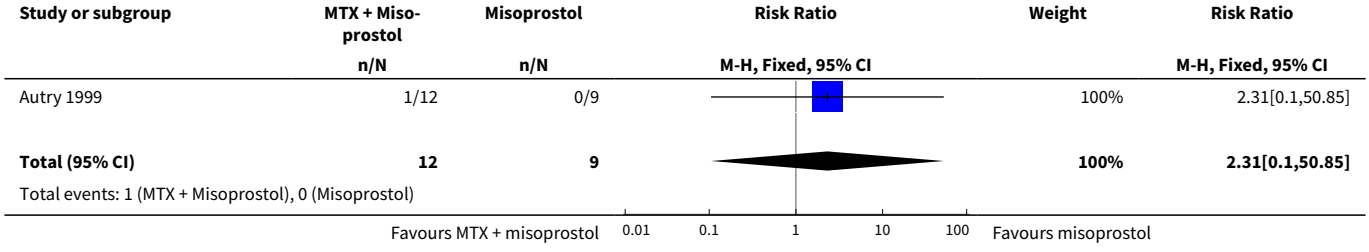
Comparison 7. Vaginal misoprostol + methotrexate versus vaginal misoprostol alone

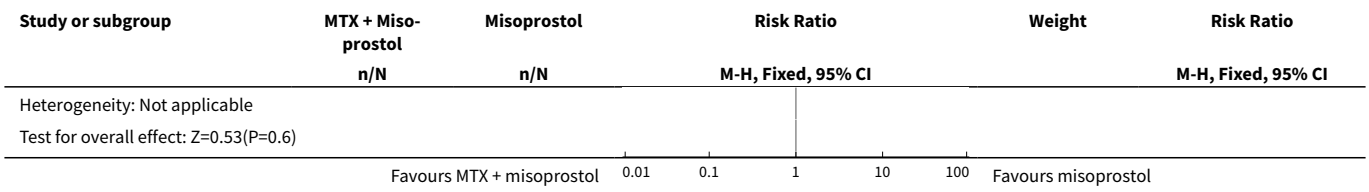
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.85, 1.50]
2 Haemorrhage	1	21	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [0.10, 50.85]
3 Pain relief	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.25, 2.22]

Analysis 7.1. Comparison 7 Vaginal misoprostol + methotrexate versus vaginal misoprostol alone, Outcome 1 Complete miscarriage.

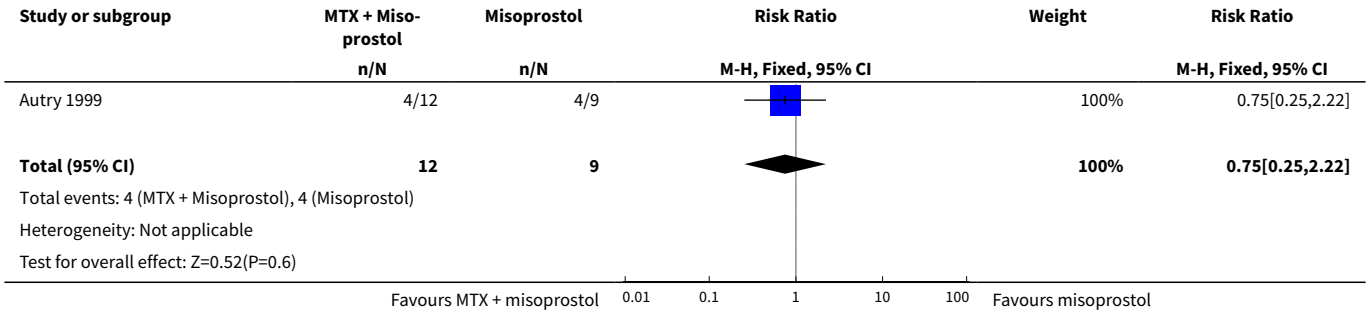


Analysis 7.2. Comparison 7 Vaginal misoprostol + methotrexate versus vaginal misoprostol alone, Outcome 2 Haemorrhage.





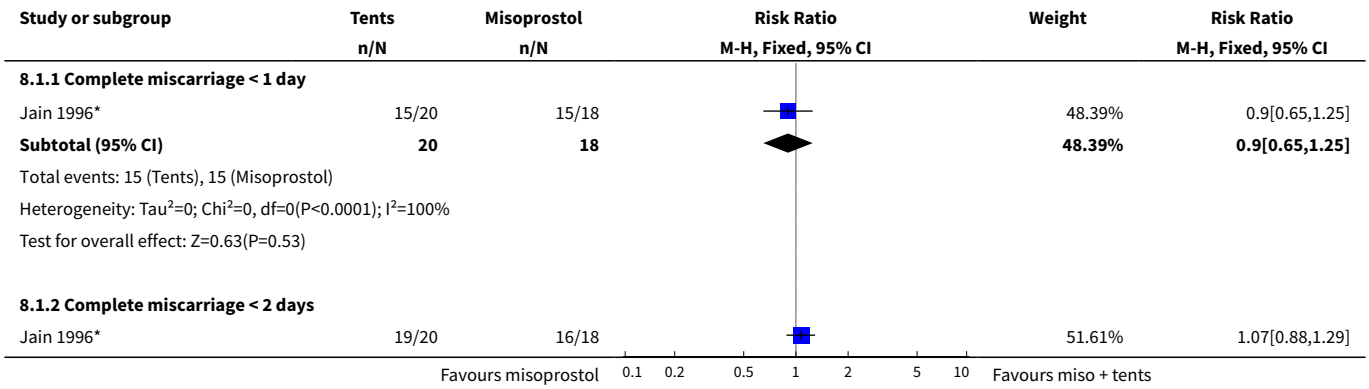
Analysis 7.3. Comparison 7 Vaginal misoprostol + methotrexate versus vaginal misoprostol alone, Outcome 3 Pain relief.

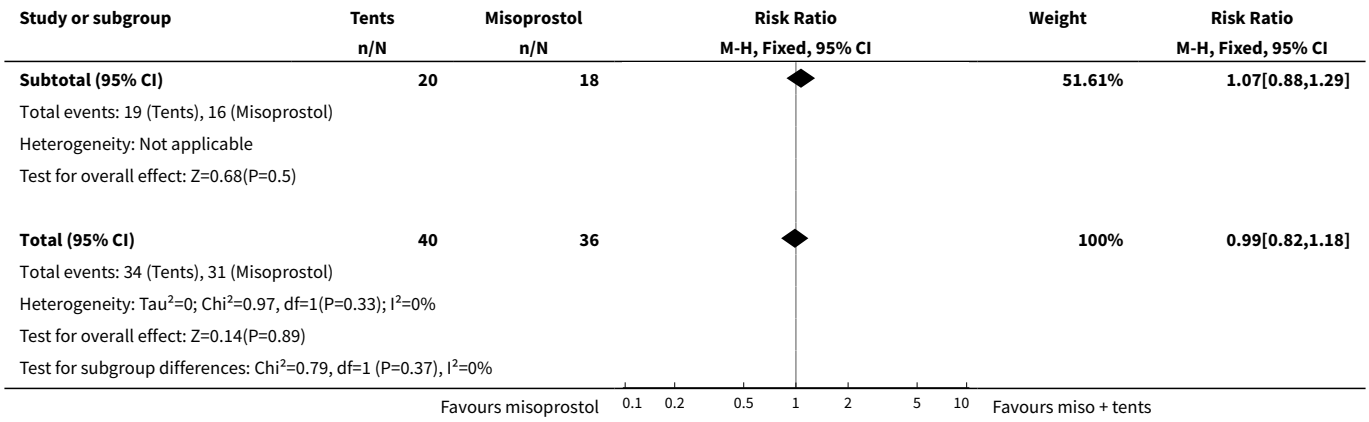


Comparison 8. Vaginal misoprostol plus laminaria tents versus vaginal misoprostol alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.82, 1.18]
1.1 Complete miscarriage < 1 day	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.25]
1.2 Complete miscarriage < 2 days	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.29]

Analysis 8.1. Comparison 8 Vaginal misoprostol plus laminaria tents versus vaginal misoprostol alone, Outcome 1 Complete miscarriage.

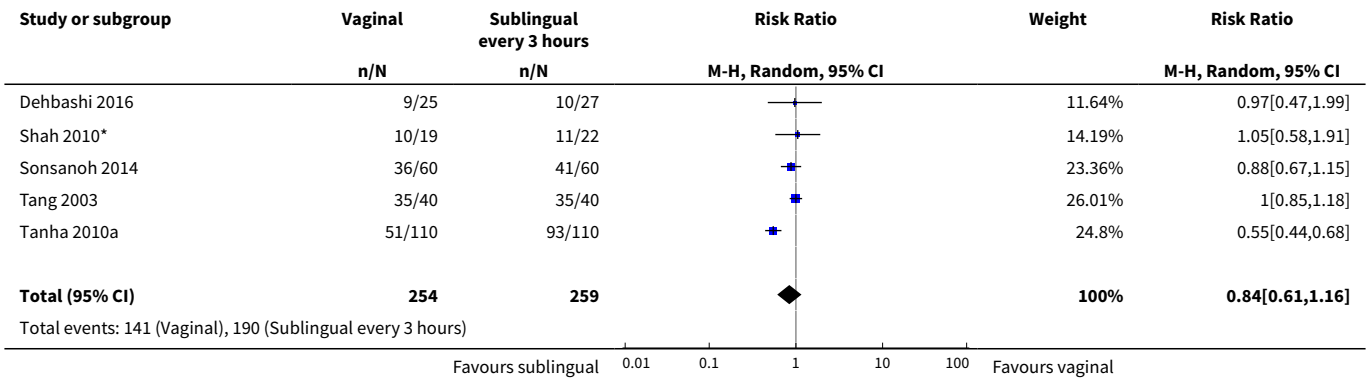


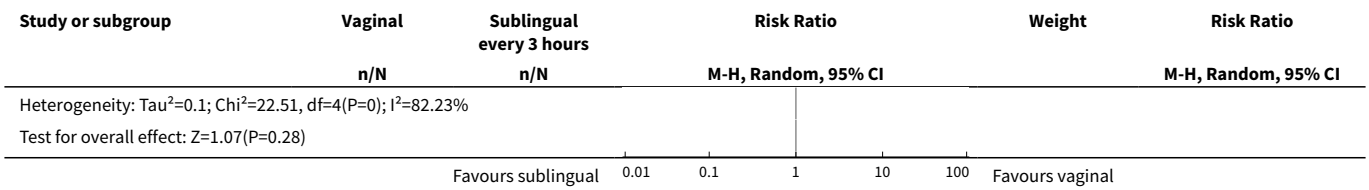


Comparison 9. Vaginal misoprostol versus sublingual misoprostol

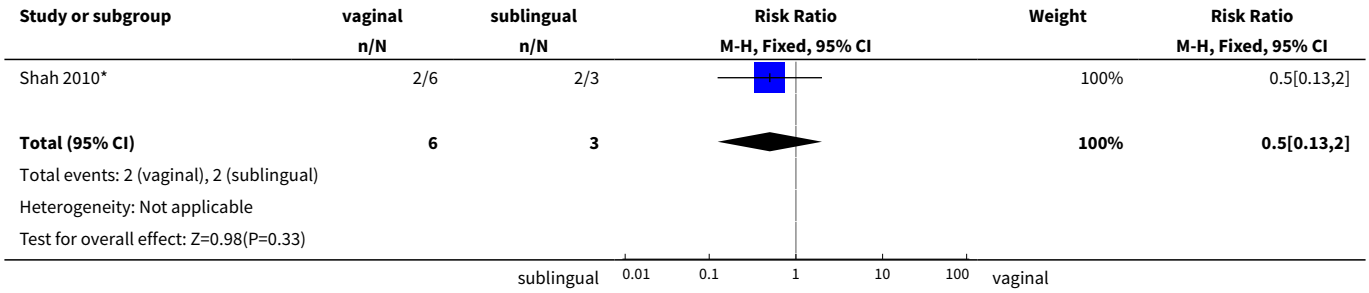
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage < 13 weeks	5	513	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.61, 1.16]
2 Complete miscarriage 13-23 weeks	1	9	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.13, 2.00]
3 Blood loss: excessive (> menstruation)	2	340	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.15, 1.89]
4 Pain	3	392	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.46, 0.74]
5 Nausea	4	302	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.12, 1.44]
6 Vomiting	2	300	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.46, 1.26]
7 Diarrhoea	4	472	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.54, 0.92]

Analysis 9.1. Comparison 9 Vaginal misoprostol versus sublingual misoprostol, Outcome 1 Complete miscarriage < 13 weeks.

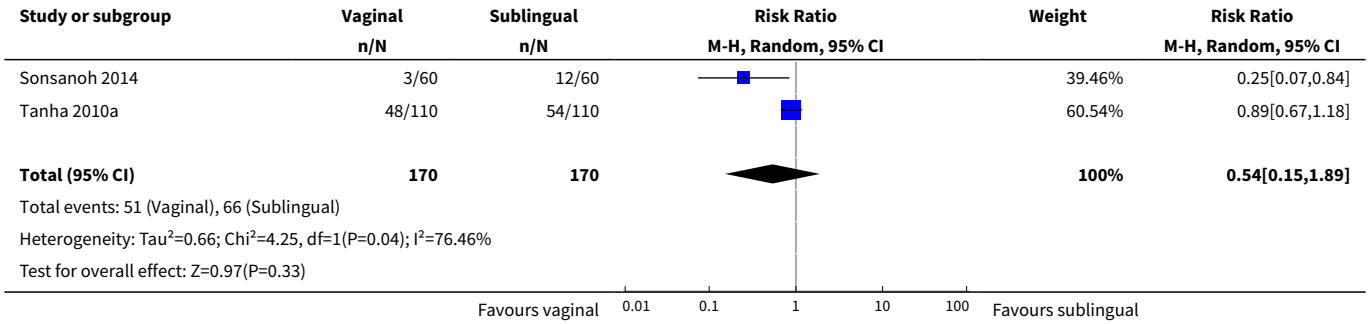




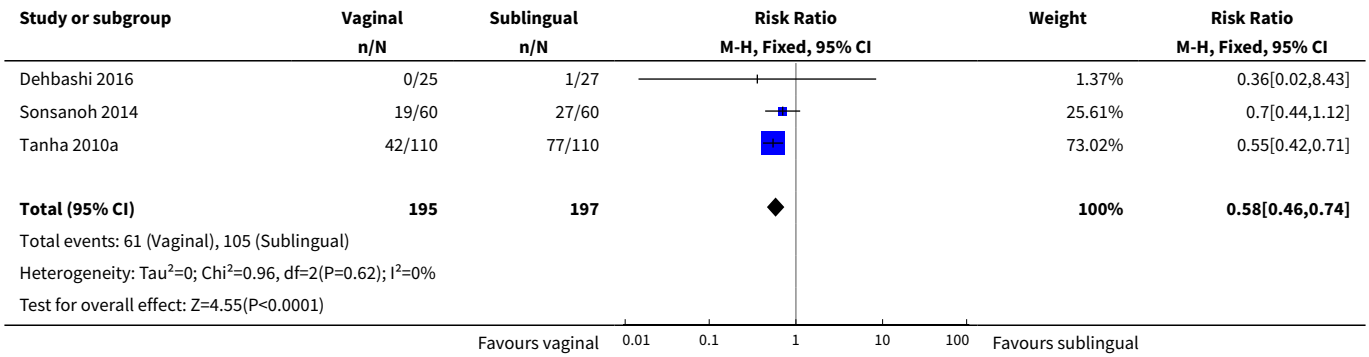
Analysis 9.2. Comparison 9 Vaginal misoprostol versus sublingual misoprostol, Outcome 2 Complete miscarriage 13-23 weeks.



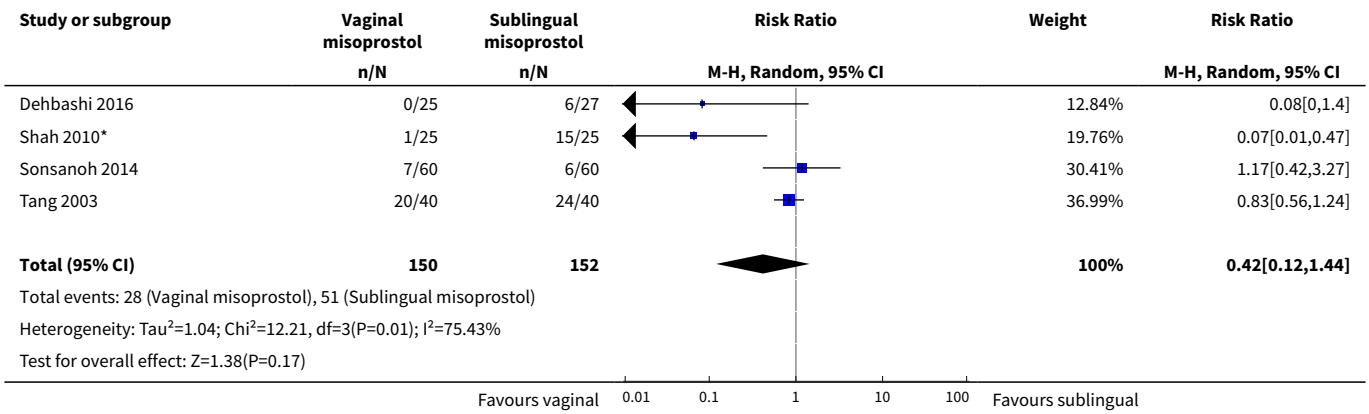
Analysis 9.3. Comparison 9 Vaginal misoprostol versus sublingual misoprostol, Outcome 3 Blood loss: excessive (> menstruation).



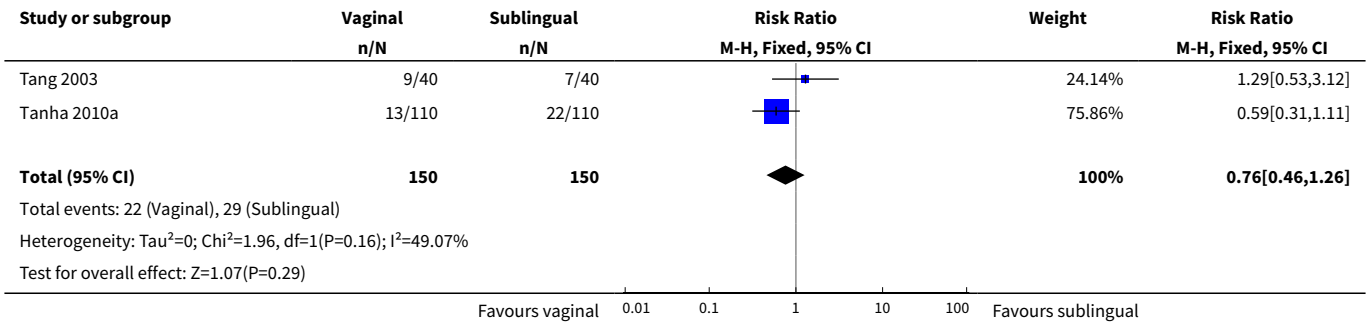
Analysis 9.4. Comparison 9 Vaginal misoprostol versus sublingual misoprostol, Outcome 4 Pain.



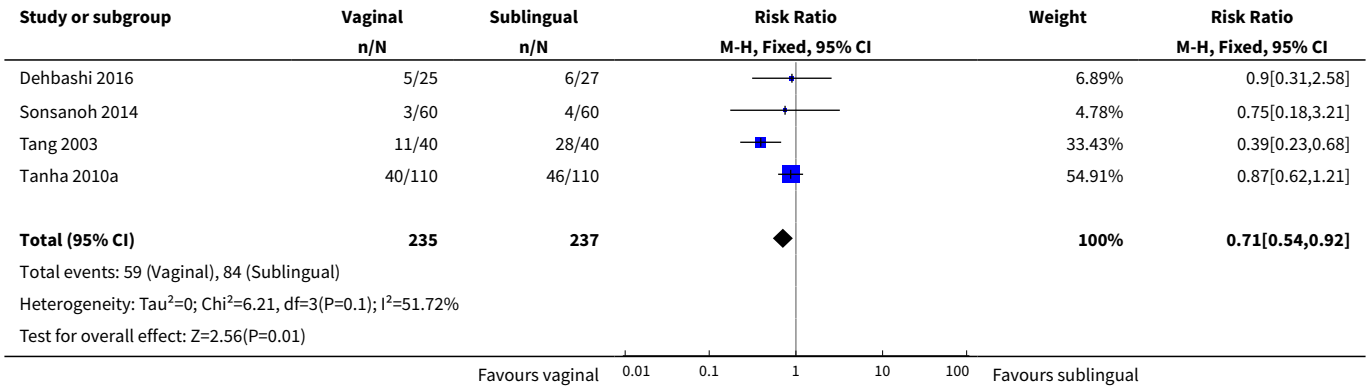
Analysis 9.5. Comparison 9 Vaginal misoprostol versus sublingual misoprostol, Outcome 5 Nausea.



Analysis 9.6. Comparison 9 Vaginal misoprostol versus sublingual misoprostol, Outcome 6 Vomiting.



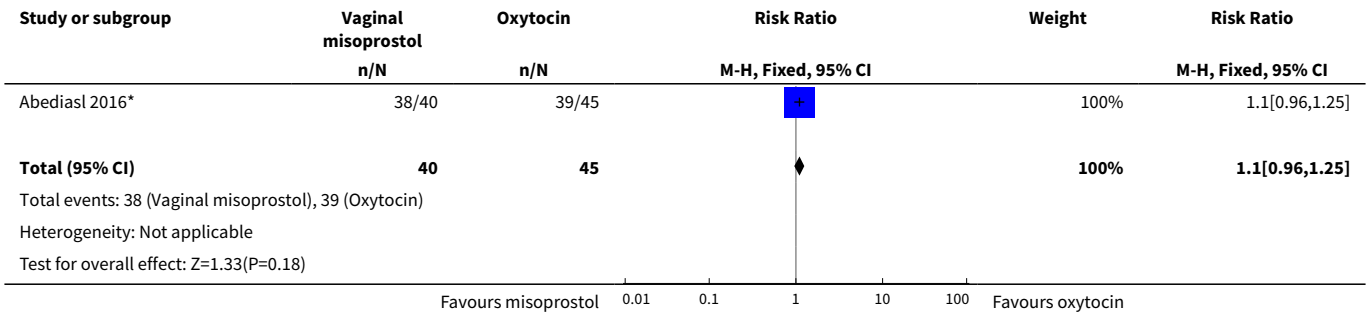
Analysis 9.7. Comparison 9 Vaginal misoprostol versus sublingual misoprostol, Outcome 7 Diarrhoea.



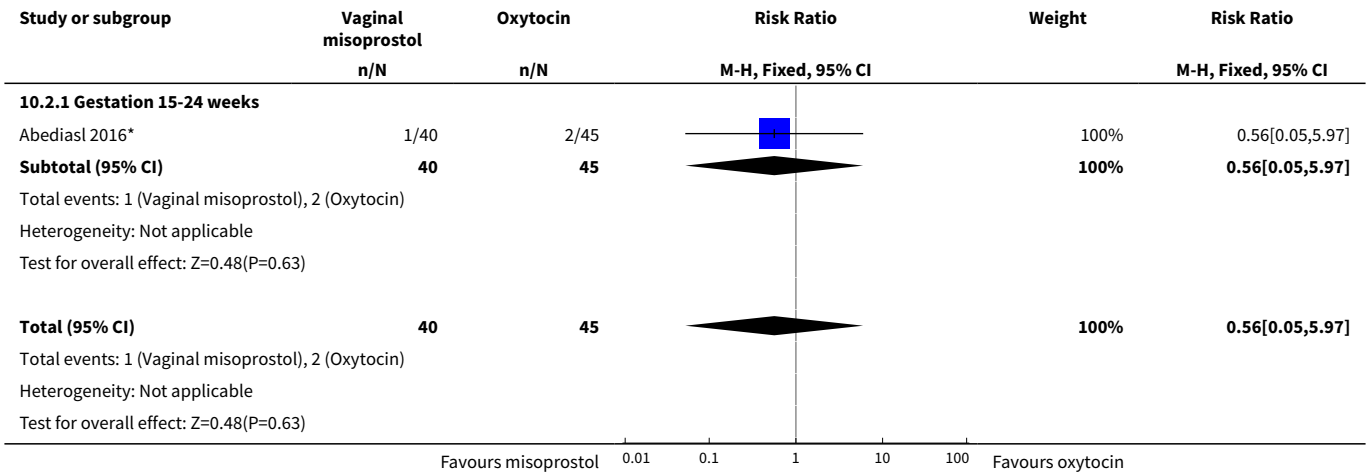
Comparison 10. Vaginal misoprostol versus intravenous oxytocin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage 13-23 weeks	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.96, 1.25]
2 Blood loss: excessive	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.05, 5.97]
2.1 Gestation 15-24 weeks	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.05, 5.97]

Analysis 10.1. Comparison 10 Vaginal misoprostol versus intravenous oxytocin, Outcome 1 Complete miscarriage 13-23 weeks.



Analysis 10.2. Comparison 10 Vaginal misoprostol versus intravenous oxytocin, Outcome 2 Blood loss: excessive.

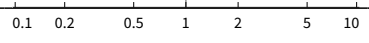


Comparison 11. Vaginal misoprostol versus vaginal gemeprost

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage 13-23 weeks	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.90, 1.70]
2 Opiates for pain relief	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Vomiting	1	50	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.30]
4 Diarrhoea	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.63]

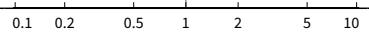
Analysis 11.1. Comparison 11 Vaginal misoprostol versus vaginal gemeprost, Outcome 1 Complete miscarriage 13-23 weeks.

Study or subgroup	Misoprostol n/N	Gemeprost n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Eng 1997*	21/25	17/25		100%	1.24[0.9,1.7]
Total (95% CI)	**25**	**25**		**100%**	**1.24[0.9,1.7]**
Total events: 21 (Misoprostol), 17 (Gemeprost)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					



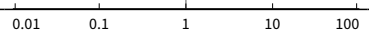
Analysis 11.2. Comparison 11 Vaginal misoprostol versus vaginal gemeprost, Outcome 2 Opiates for pain relief.

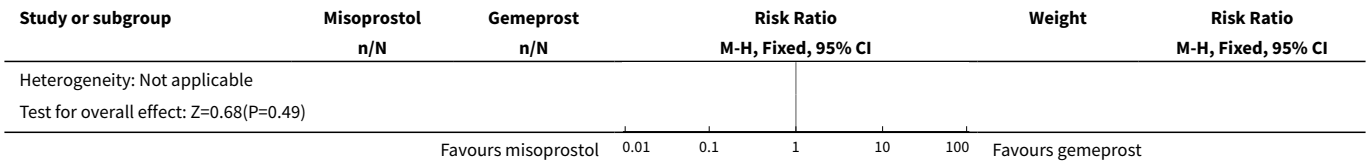
Study or subgroup	Misoprostol n/N	Gemeprost n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Eng 1997*	0/25	0/25			Not estimable
Total (95% CI)	**25**	**25**			**Not estimable**
Total events: 0 (Misoprostol), 0 (Gemeprost)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



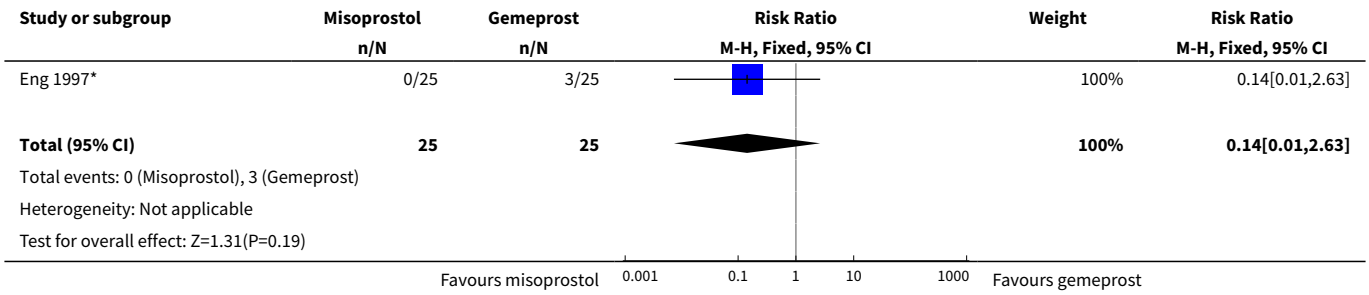
Analysis 11.3. Comparison 11 Vaginal misoprostol versus vaginal gemeprost, Outcome 3 Vomiting.

Study or subgroup	Misoprostol n/N	Gemeprost n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Eng 1997*	1/25	0/25		100%	3[0.13,70.3]
Total (95% CI)	**25**	**25**		**100%**	**3[0.13,70.3]**
Total events: 1 (Misoprostol), 0 (Gemeprost)					





Analysis 11.4. Comparison 11 Vaginal misoprostol versus vaginal gemeprost, Outcome 4 Diarrhoea.

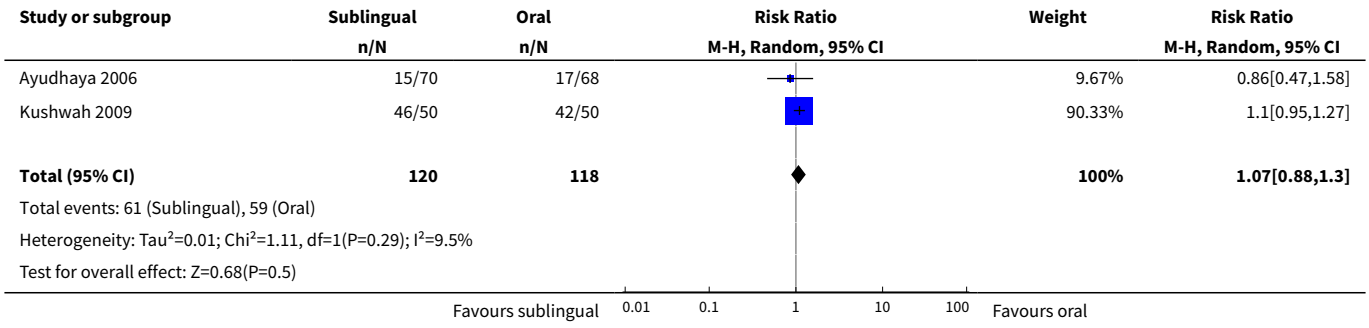


Comparison 12. Sublingual misoprostol versus oral misoprostol

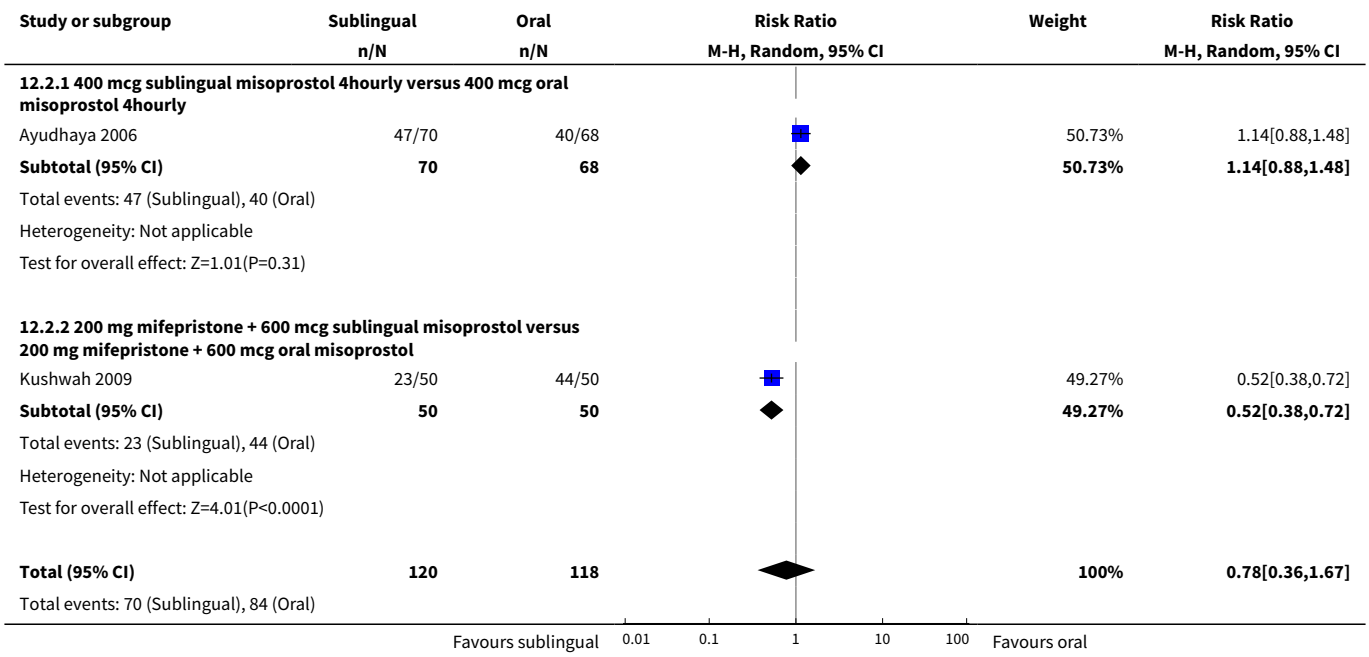
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	2	238	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.88, 1.30]
2 Pain	2	238	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.36, 1.67]
2.1 400 mcg sublingual misoprostol 4hourly versus 400 mcg oral misoprostol 4hourly	1	138	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.88, 1.48]
2.2 200 mg mifepristone + 600 mcg sublingual misoprostol versus 200 mg mifepristone + 600 mcg oral misoprostol	1	100	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.38, 0.72]
3 Nausea and/or vomiting	2	338	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.41, 0.85]
3.1 Nausea and/or vomiting	1	138	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.11, 3.76]
3.2 Nausea	1	100	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.41, 1.05]
3.3 Vomiting	1	100	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.27, 0.92]
4 Diarrhoea	2	238	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.60, 1.22]

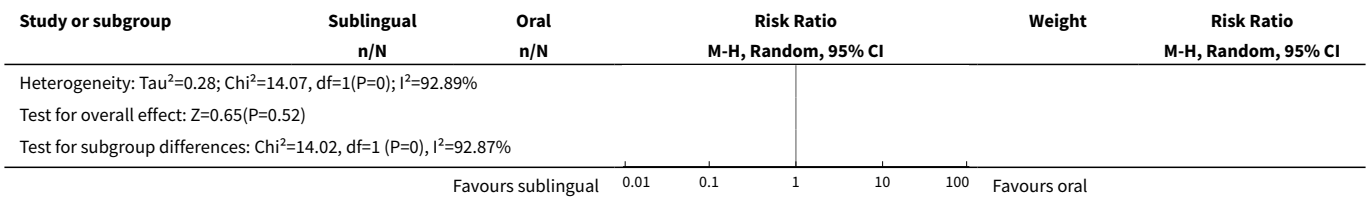
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 400 mcg sublingual misoprostol 4 hourly versus 400 mcg oral misoprostol 4 hourly	1	138	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.29, 2.35]
4.2 200 mg mifepristone + 600 mcg sublingual misoprostol versus 200 mg mifepristone + 600 mcg oral misoprostol	1	100	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.59, 1.25]
5 Woman's satisfaction with treatment	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.06, 1.55]

Analysis 12.1. Comparison 12 Sublingual misoprostol versus oral misoprostol, Outcome 1 Complete miscarriage.

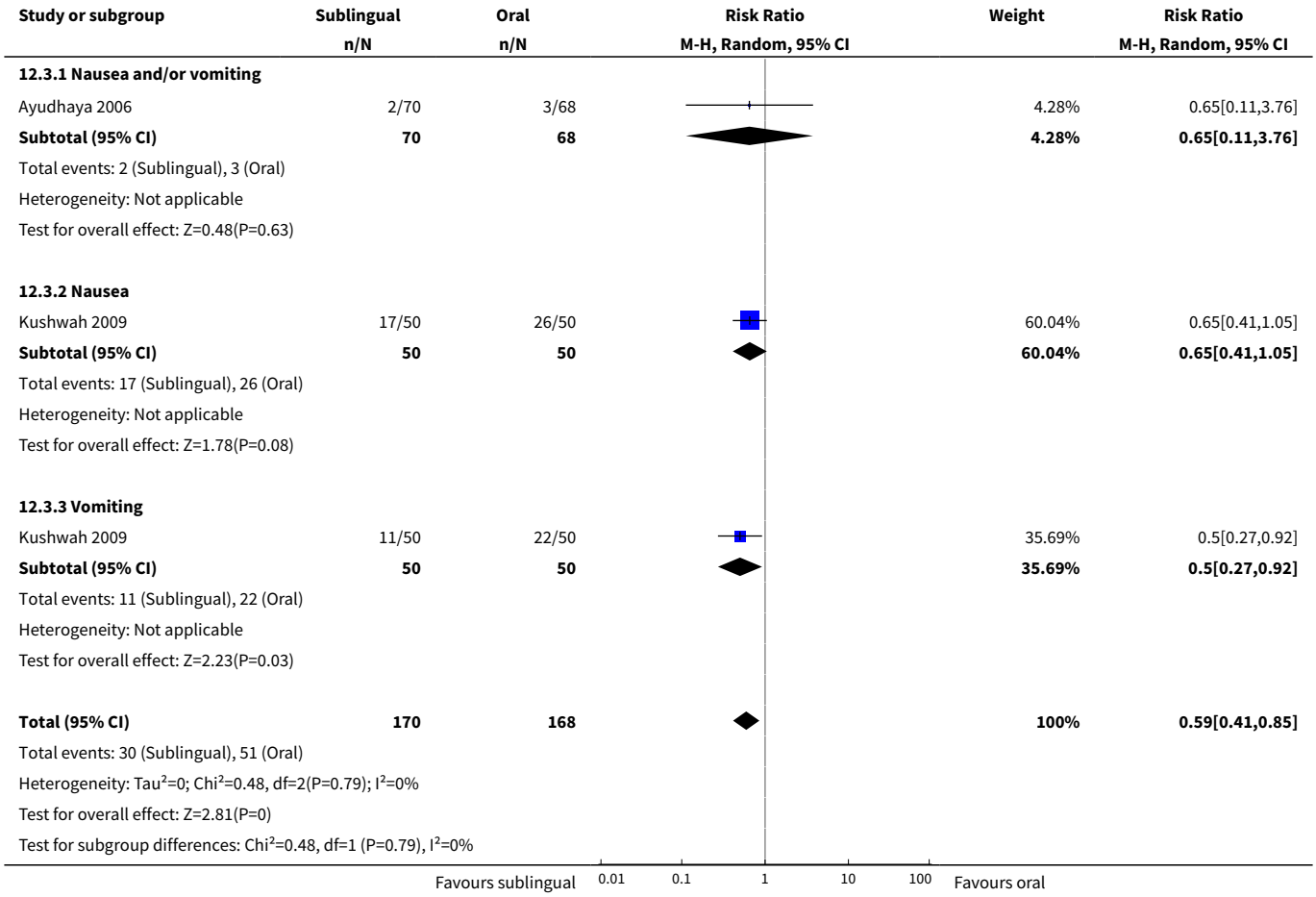


Analysis 12.2. Comparison 12 Sublingual misoprostol versus oral misoprostol, Outcome 2 Pain.

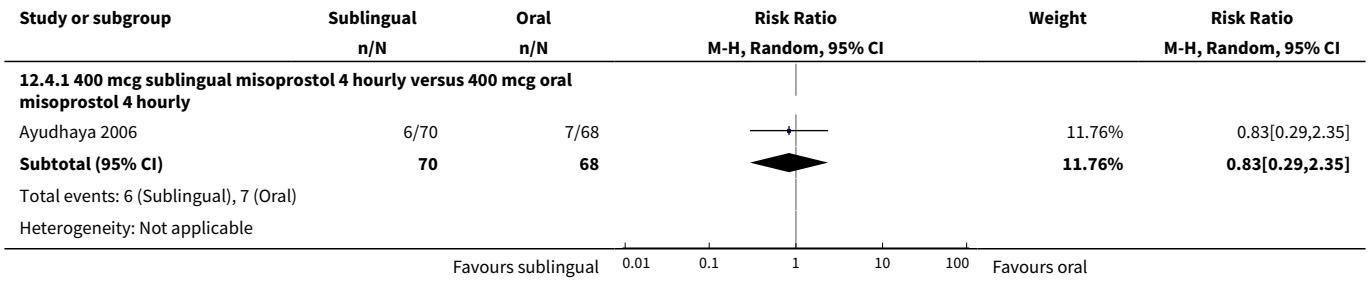


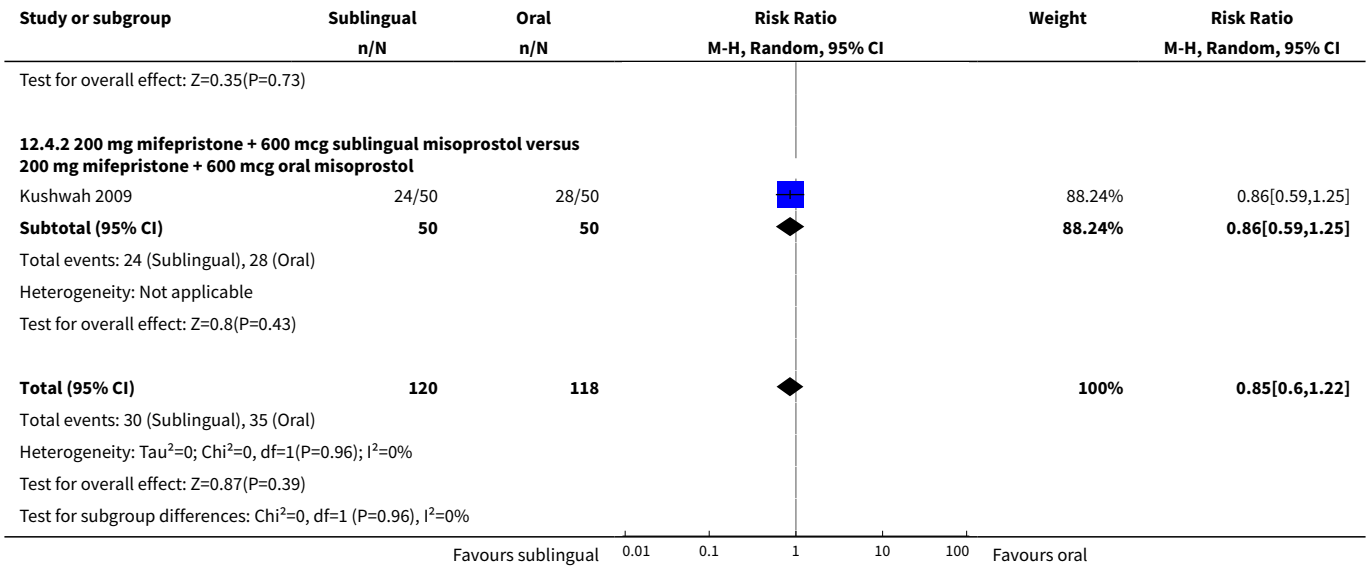


Analysis 12.3. Comparison 12 Sublingual misoprostol versus oral misoprostol, Outcome 3 Nausea and/or vomiting.

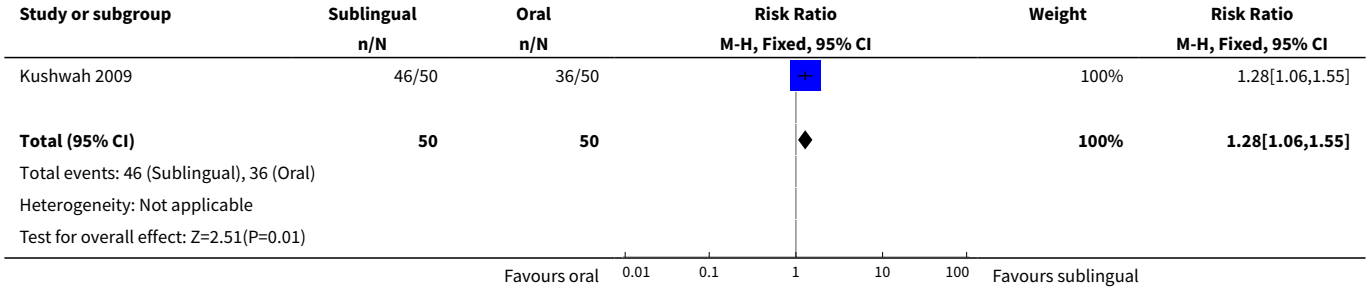


Analysis 12.4. Comparison 12 Sublingual misoprostol versus oral misoprostol, Outcome 4 Diarrhoea.





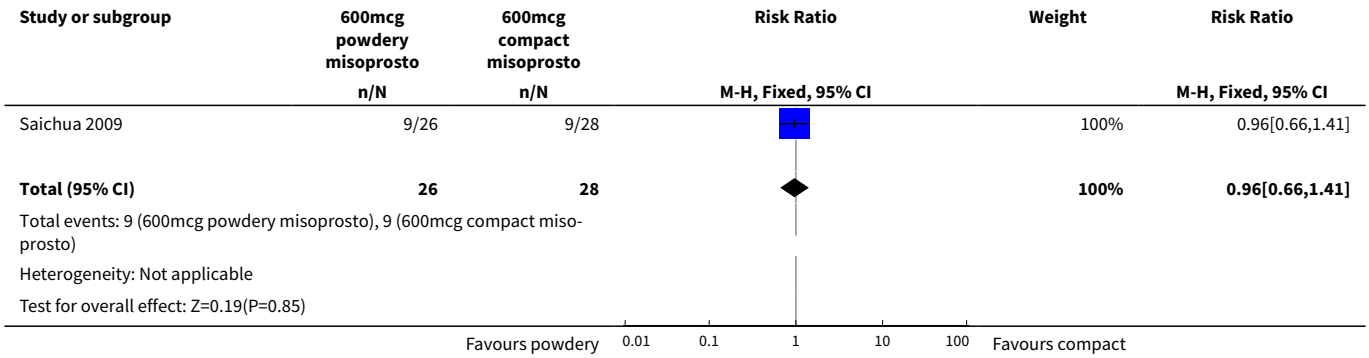
Analysis 12.5. Comparison 12 Sublingual misoprostol versus oral misoprostol, Outcome 5 Woman's satisfaction with treatment.



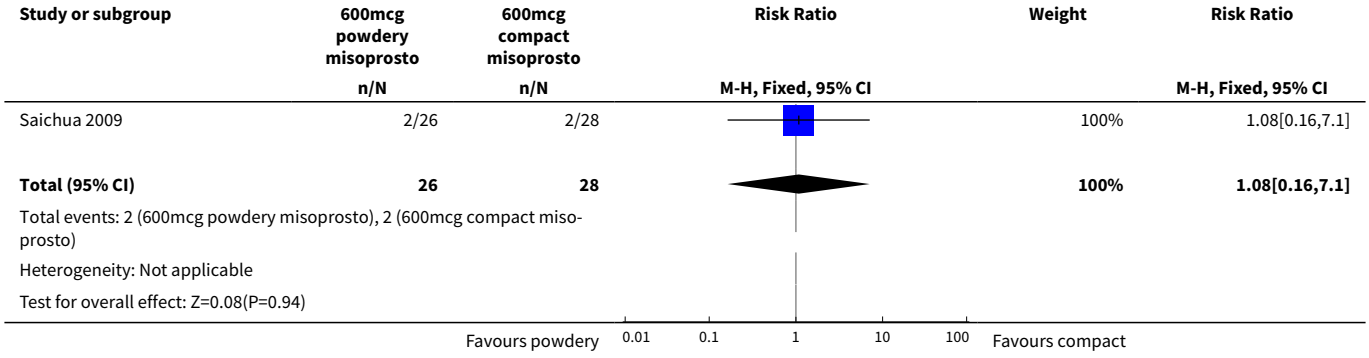
Comparison 13. Sublingual powdery versus sublingual compact misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.66, 1.41]
2 Nausea/vomiting	1	54	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.16, 7.10]
3 Diarrhoea	1	54	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.44, 2.65]

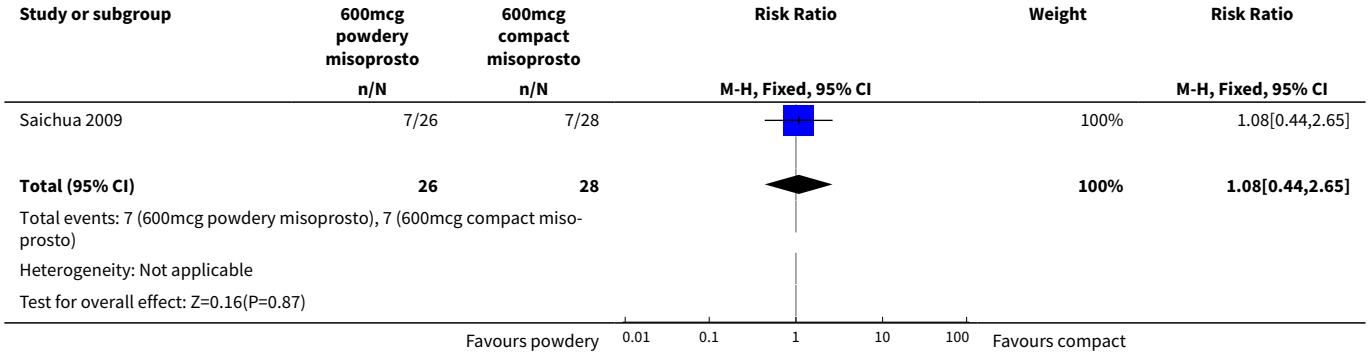
Analysis 13.1. Comparison 13 Sublingual powdery versus sublingual compact misoprostol, Outcome 1 Complete miscarriage.



Analysis 13.2. Comparison 13 Sublingual powdery versus sublingual compact misoprostol, Outcome 2 Nausea/vomiting.



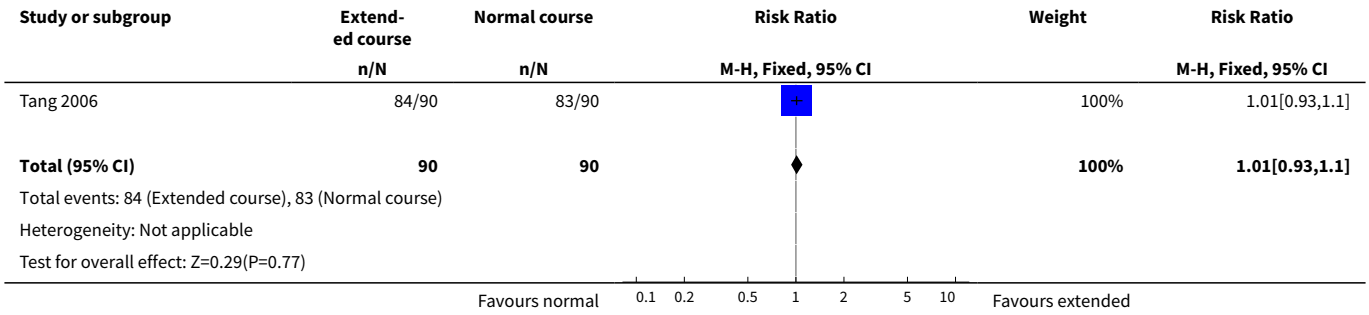
Analysis 13.3. Comparison 13 Sublingual powdery versus sublingual compact misoprostol, Outcome 3 Diarrhoea.



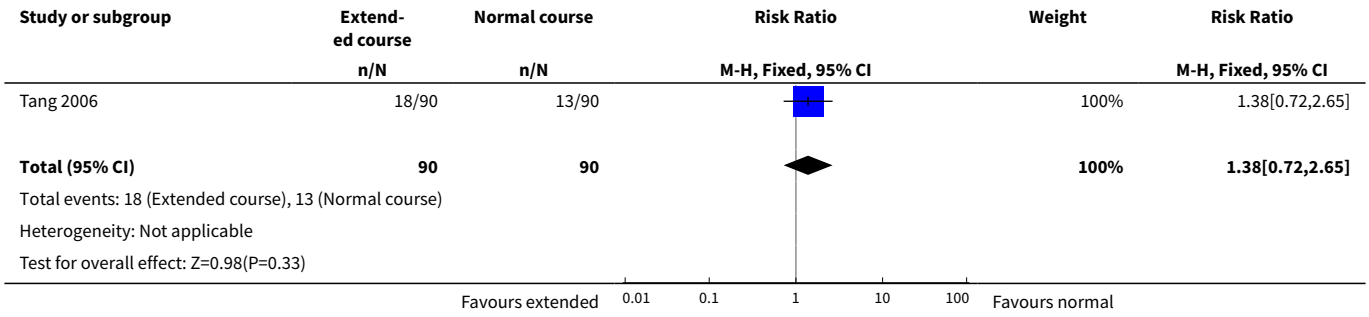
Comparison 14. Sublingual misoprostol with versus without extended course

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	1	180	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.10]
2 Nausea	1	180	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.72, 2.65]
3 Pain	1	180	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.96, 1.31]
4 Vomiting	1	180	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.60, 41.95]
5 Diarrhoea	1	180	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [1.25, 3.19]

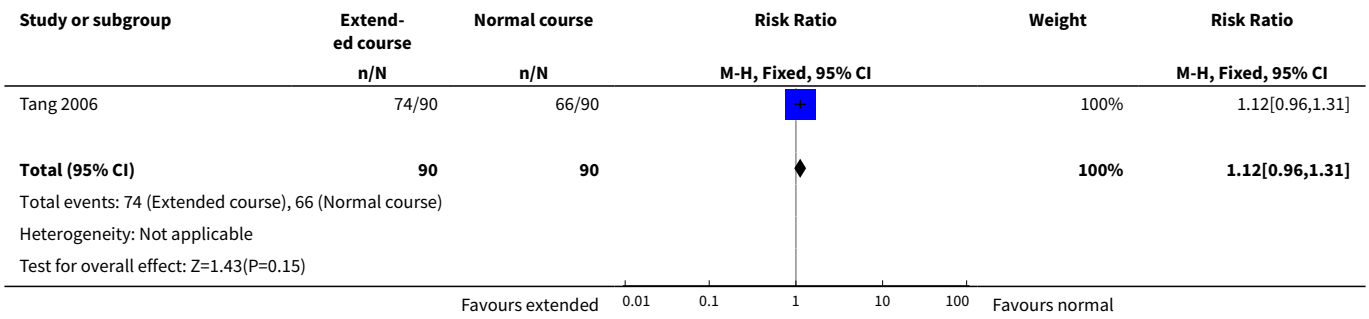
Analysis 14.1. Comparison 14 Sublingual misoprostol with versus without extended course, Outcome 1 Complete miscarriage.



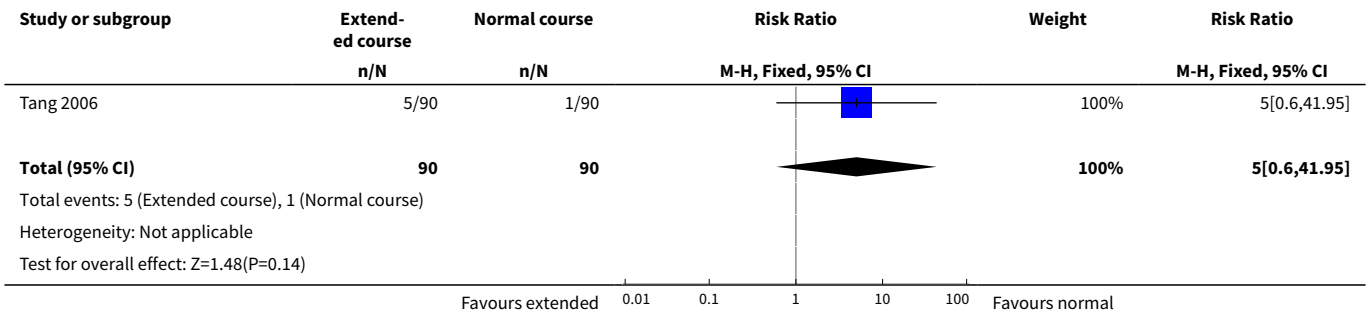
Analysis 14.2. Comparison 14 Sublingual misoprostol with versus without extended course, Outcome 2 Nausea.



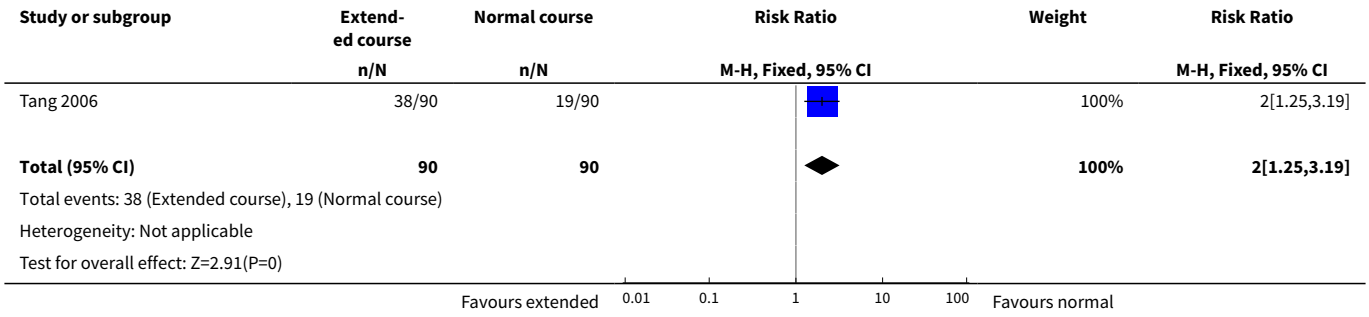
Analysis 14.3. Comparison 14 Sublingual misoprostol with versus without extended course, Outcome 3 Pain.



Analysis 14.4. Comparison 14 Sublingual misoprostol with versus without extended course, Outcome 4 Vomiting.



Analysis 14.5. Comparison 14 Sublingual misoprostol with versus without extended course, Outcome 5 Diarrhoea.

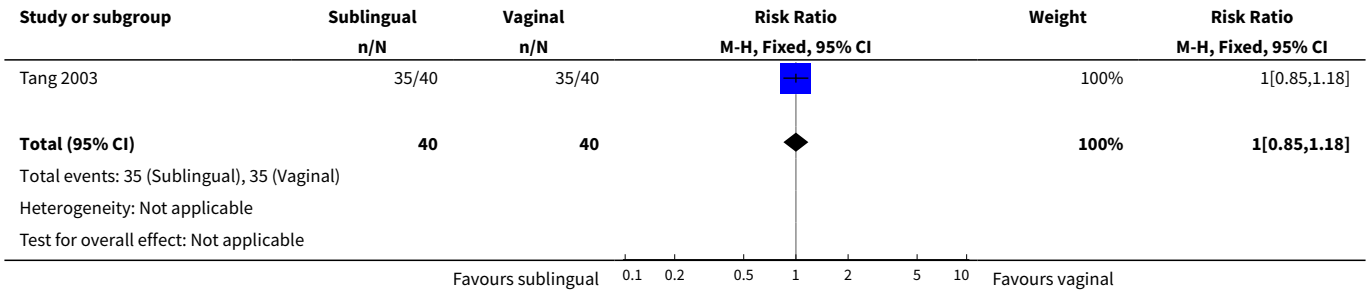


Comparison 15. Sublingual + vaginal misoprostol versus only vaginal misoprostol

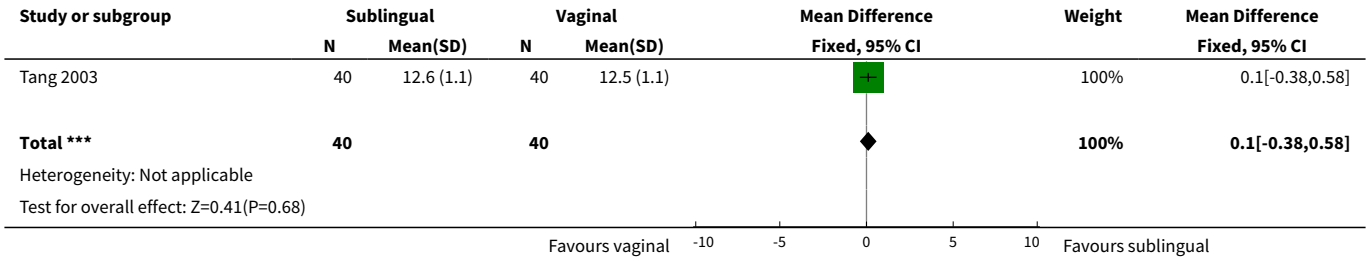
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.85, 1.18]
2 Blood loss: haemoglobin level	1	80	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.38, 0.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Nausea	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.80, 1.79]
4 Vomiting	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.32, 1.88]
5 Diarrhoea	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.55 [1.48, 4.38]
6 Pain	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.29, 1.97]
7 Woman's satisfaction with treatment	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.79, 1.25]

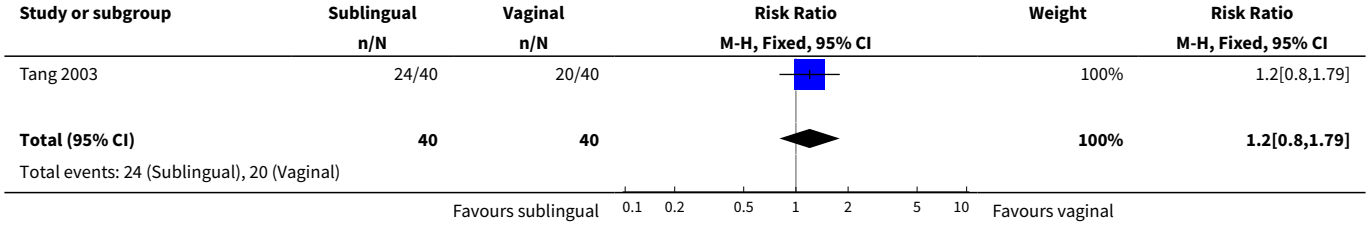
Analysis 15.1. Comparison 15 Sublingual + vaginal misoprostol versus only vaginal misoprostol, Outcome 1 Complete miscarriage.

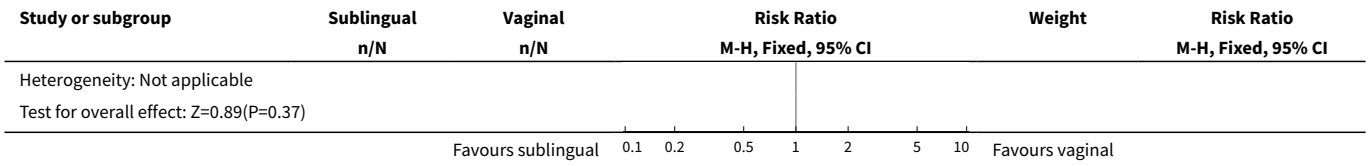


Analysis 15.2. Comparison 15 Sublingual + vaginal misoprostol versus only vaginal misoprostol, Outcome 2 Blood loss: haemoglobin level.

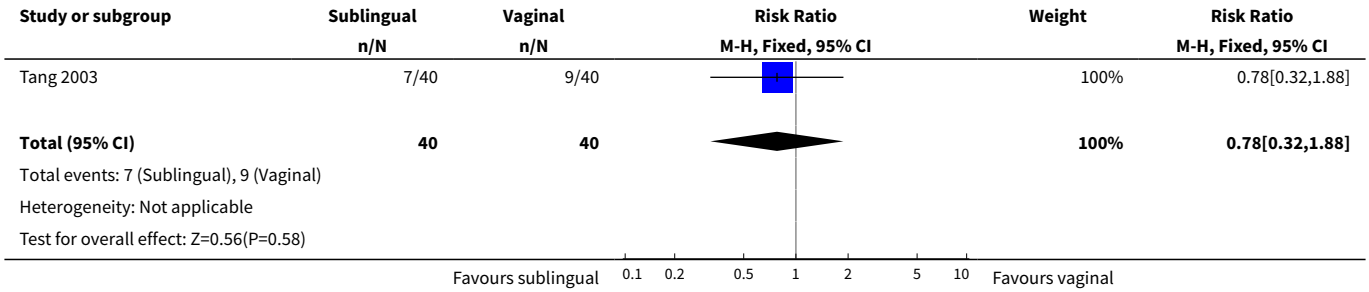


Analysis 15.3. Comparison 15 Sublingual + vaginal misoprostol versus only vaginal misoprostol, Outcome 3 Nausea.

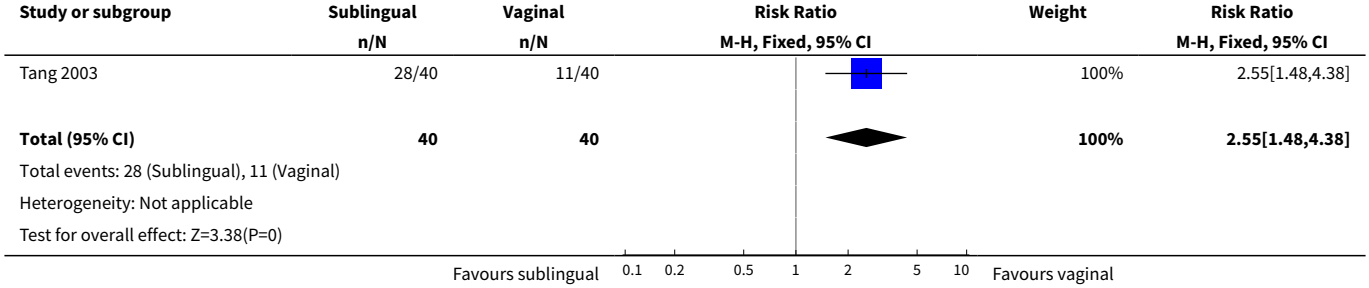




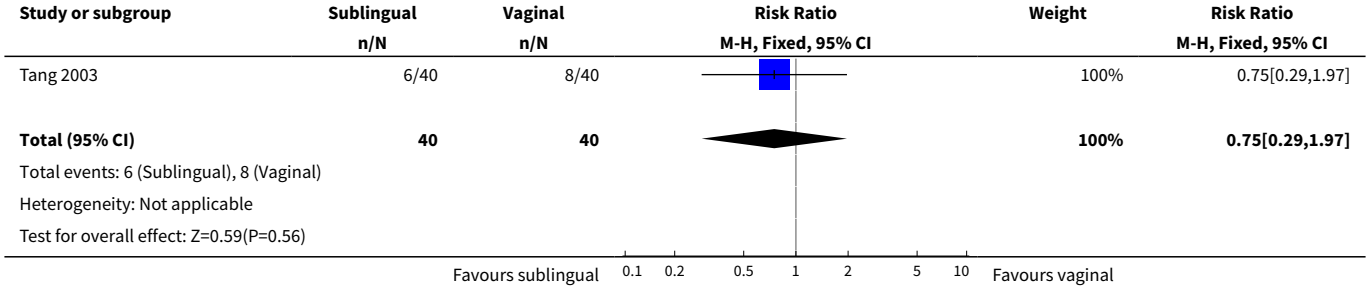
Analysis 15.4. Comparison 15 Sublingual + vaginal misoprostol versus only vaginal misoprostol, Outcome 4 Vomiting.



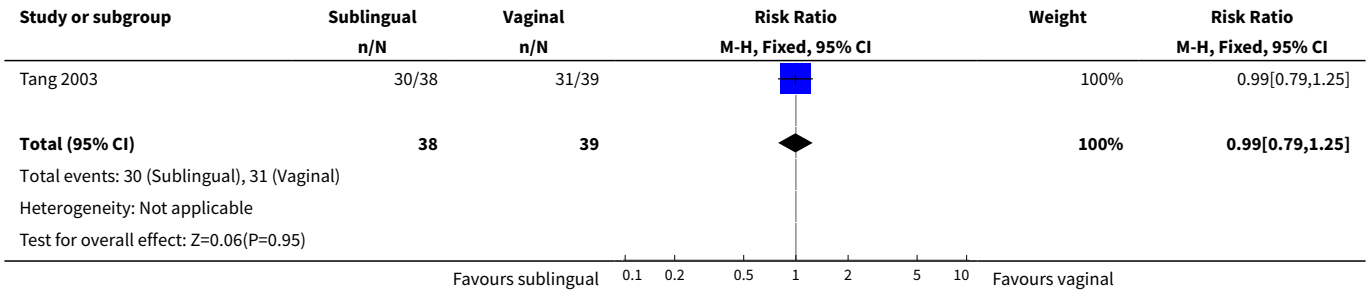
Analysis 15.5. Comparison 15 Sublingual + vaginal misoprostol versus only vaginal misoprostol, Outcome 5 Diarrhoea.



Analysis 15.6. Comparison 15 Sublingual + vaginal misoprostol versus only vaginal misoprostol, Outcome 6 Pain.



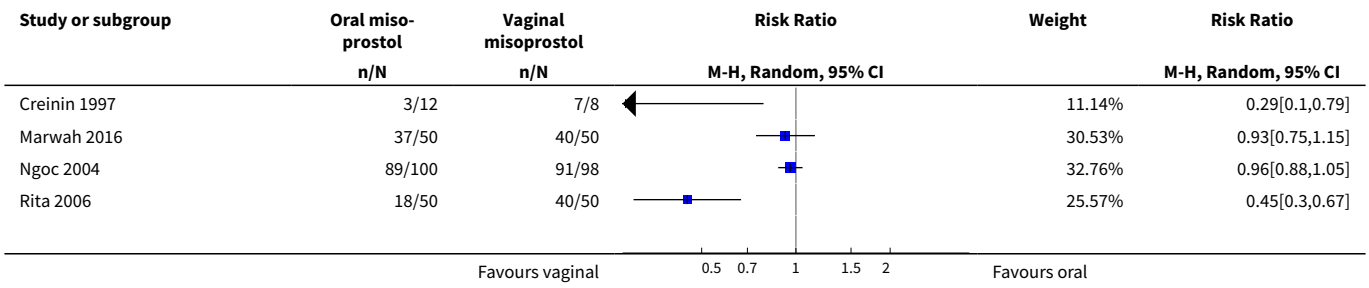
Analysis 15.7. Comparison 15 Sublingual + vaginal misoprostol versus only vaginal misoprostol, Outcome 7 Woman's satisfaction with treatment.

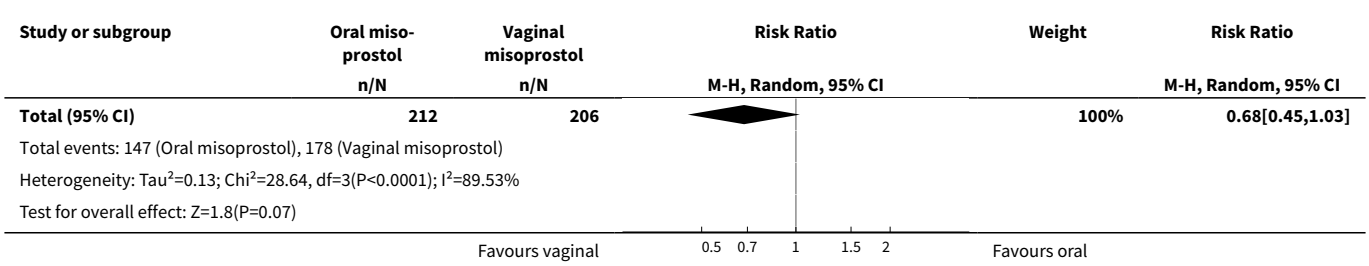


Comparison 16. Oral misoprostol versus vaginal misoprostol

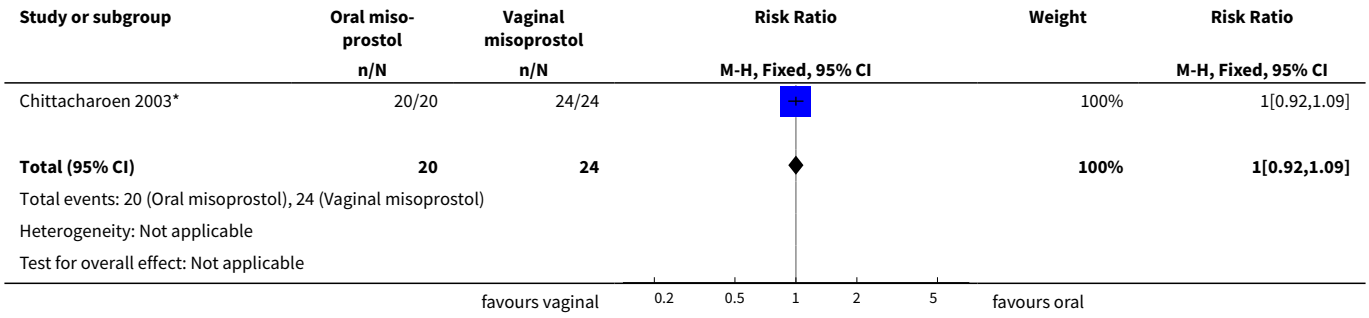
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage < 13 weeks	4	418	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.45, 1.03]
2 Complete miscarriage > 13-23 weeks	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.92, 1.09]
3 Blood loss: excessive	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.32, 27.87]
4 Pain (visual analogue scale)	1	18	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-4.82, 1.02]
5 Pain	2	200	Risk Ratio (M-H, Fixed, 95% CI)	1.6 [1.01, 2.55]
6 Vomiting	2	290	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.11, 4.89]
7 Nausea	3	220	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.93, 1.48]
8 Diarrhoea	4	410	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.72, 1.58]
9 Woman's satisfaction with treatment	1	198	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.86, 1.06]

Analysis 16.1. Comparison 16 Oral misoprostol versus vaginal misoprostol, Outcome 1 Complete miscarriage < 13 weeks.

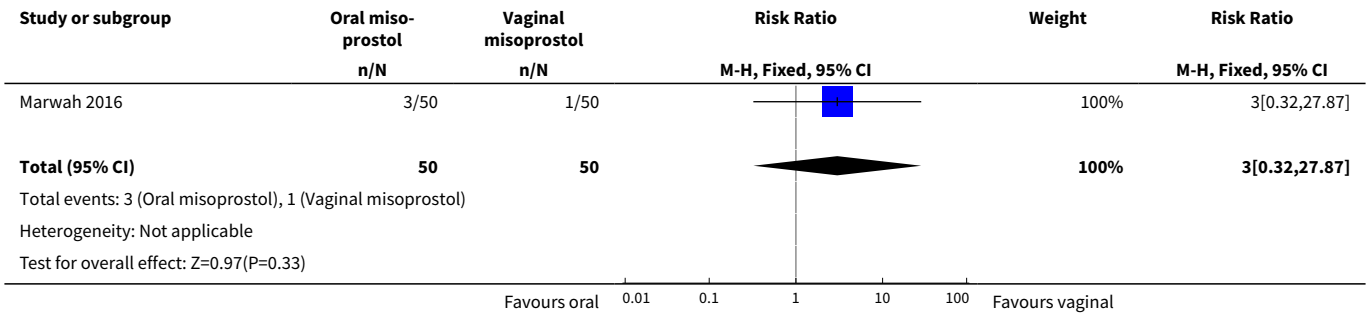




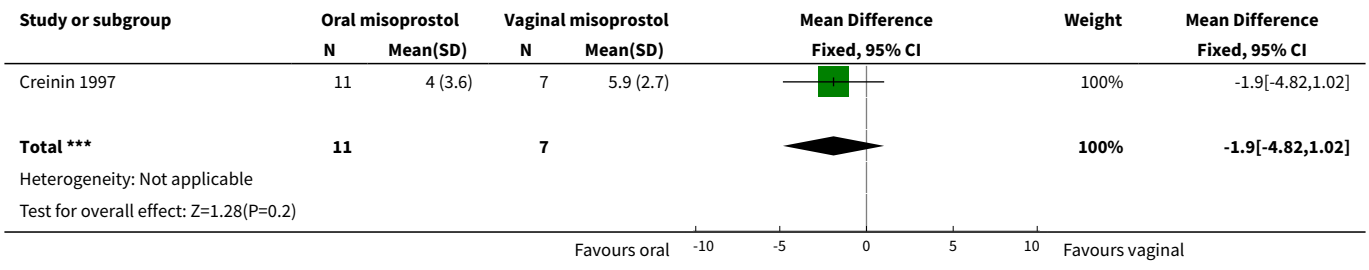
Analysis 16.2. Comparison 16 Oral misoprostol versus vaginal misoprostol, Outcome 2 Complete miscarriage > 13-23 weeks.



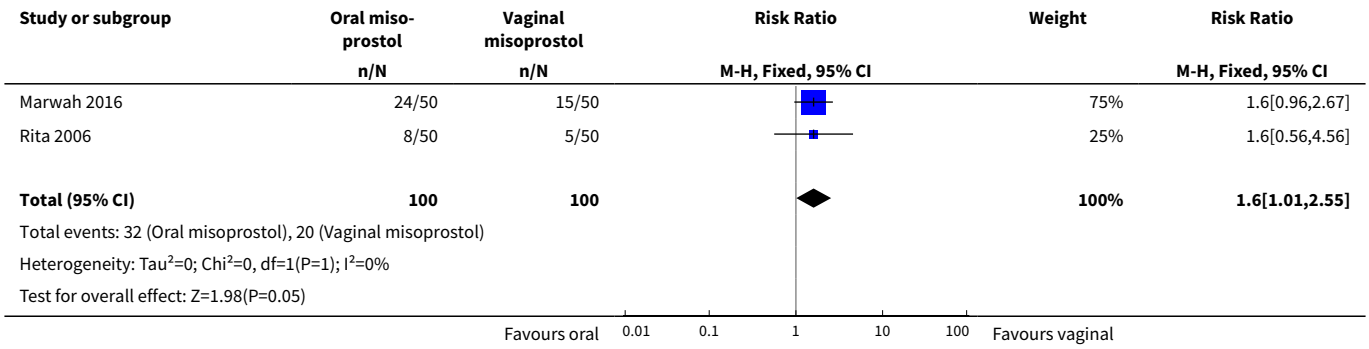
Analysis 16.3. Comparison 16 Oral misoprostol versus vaginal misoprostol, Outcome 3 Blood loss: excessive.



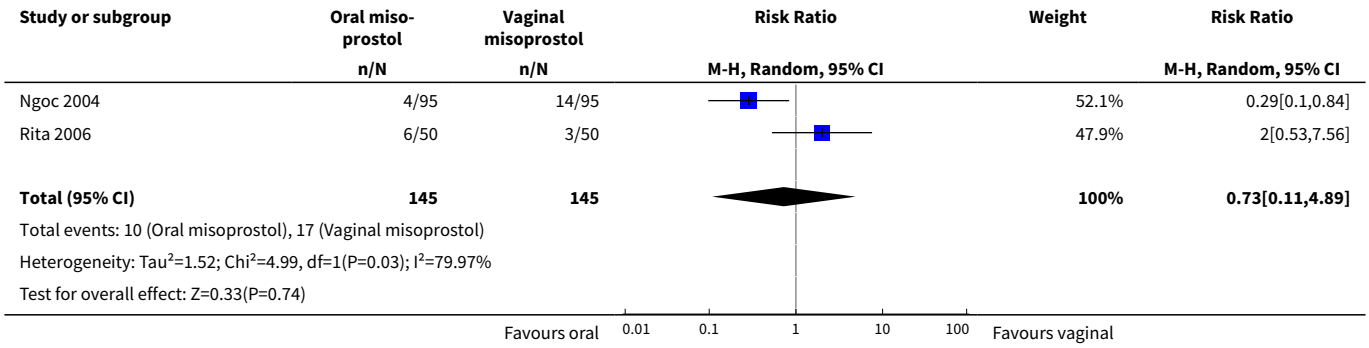
Analysis 16.4. Comparison 16 Oral misoprostol versus vaginal misoprostol, Outcome 4 Pain (visual analogue scale).



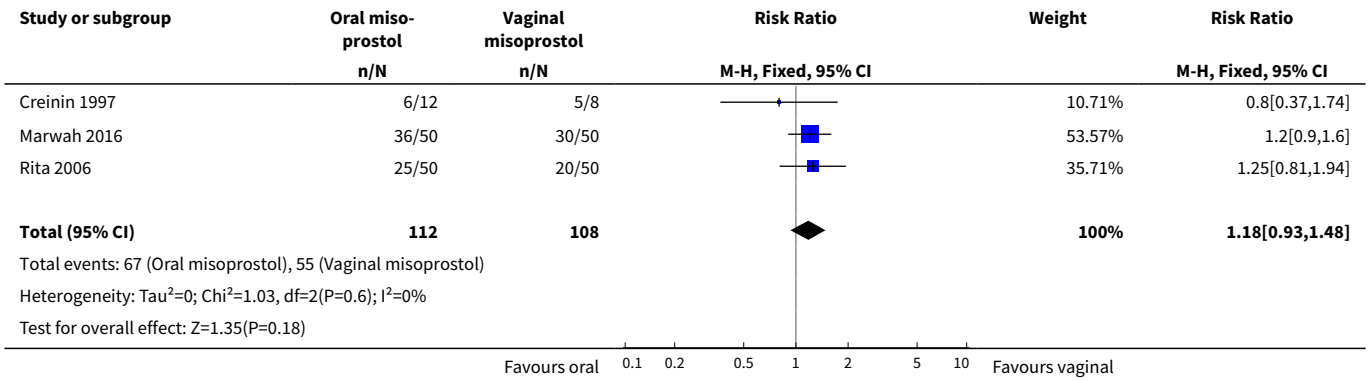
Analysis 16.5. Comparison 16 Oral misoprostol versus vaginal misoprostol, Outcome 5 Pain.



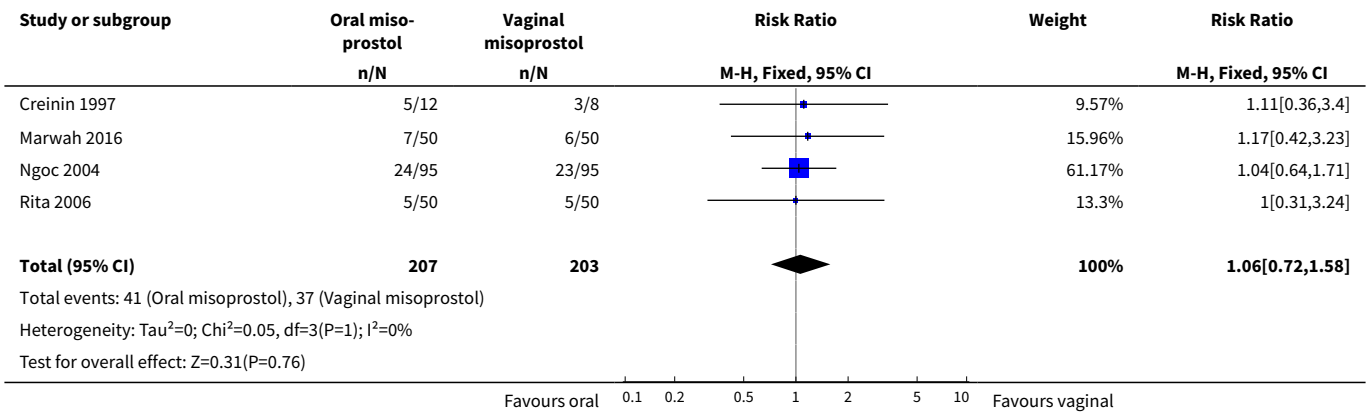
Analysis 16.6. Comparison 16 Oral misoprostol versus vaginal misoprostol, Outcome 6 Vomiting.



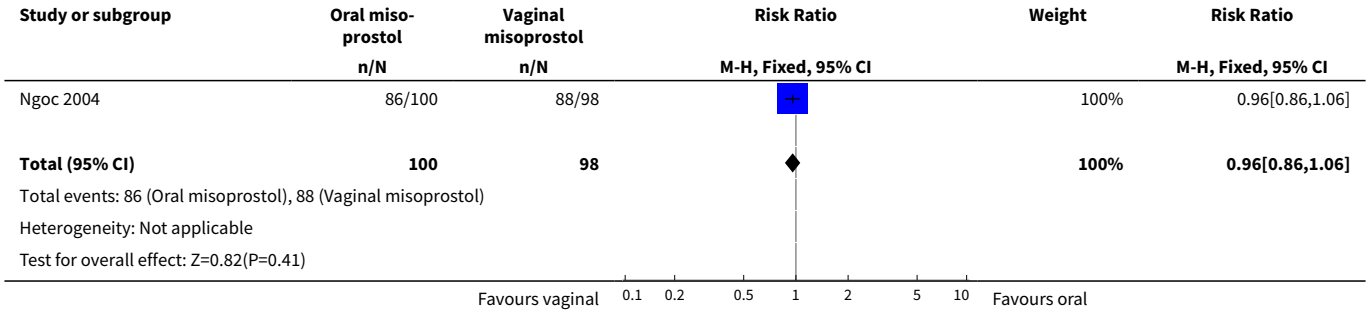
Analysis 16.7. Comparison 16 Oral misoprostol versus vaginal misoprostol, Outcome 7 Nausea.



Analysis 16.8. Comparison 16 Oral misoprostol versus vaginal misoprostol, Outcome 8 Diarrhoea.



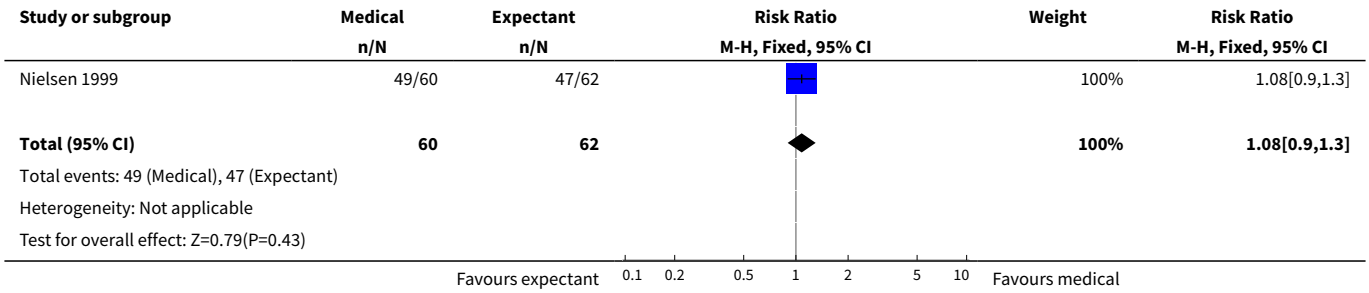
Analysis 16.9. Comparison 16 Oral misoprostol versus vaginal misoprostol, Outcome 9 Woman's satisfaction with treatment.



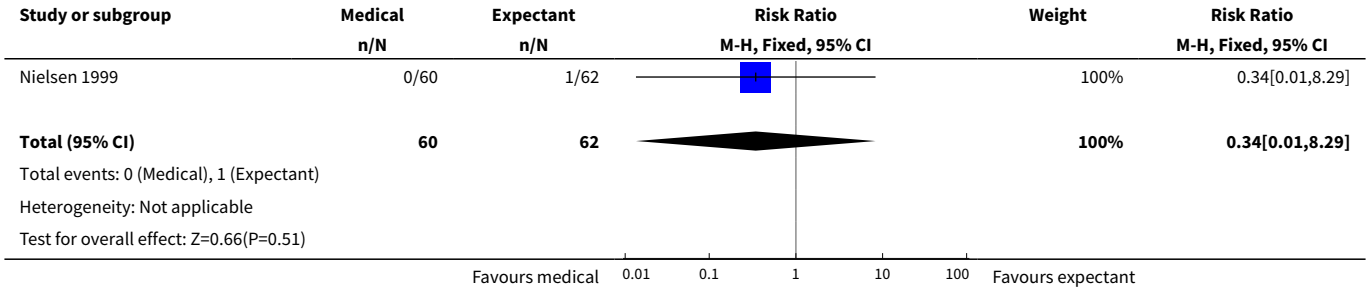
Comparison 17. Oral misoprostol + mifepristone versus expectant management

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	1	122	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.90, 1.30]
2 Blood loss (severe)	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.29]
3 Days of bleeding	1	122	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.43, 1.83]
4 Pain	1	122	Mean Difference (IV, Fixed, 95% CI)	4.10 [-5.92, 14.12]
5 Pelvic infection	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.55]
6 Woman's satisfaction with treatment (visual analogue scale day 14)	1	122	Mean Difference (IV, Fixed, 95% CI)	3.40 [-5.54, 12.34]

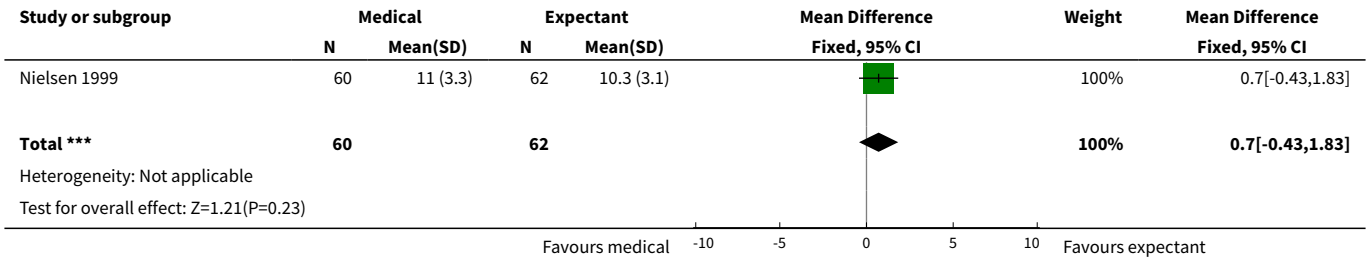
Analysis 17.1. Comparison 17 Oral misoprostol + mifepristone versus expectant management, Outcome 1 Complete miscarriage.



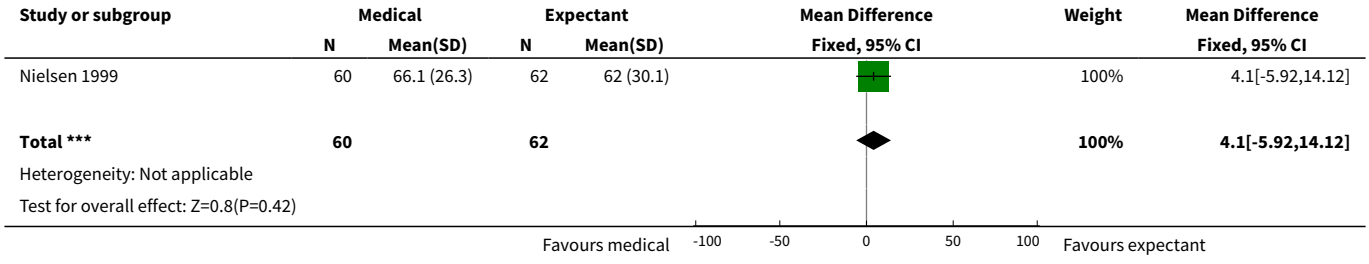
Analysis 17.2. Comparison 17 Oral misoprostol + mifepristone versus expectant management, Outcome 2 Blood loss (severe).



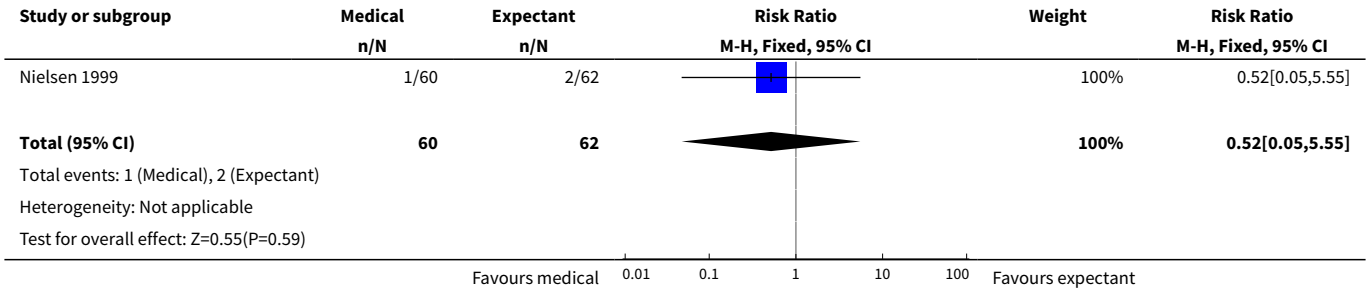
Analysis 17.3. Comparison 17 Oral misoprostol + mifepristone versus expectant management, Outcome 3 Days of bleeding.



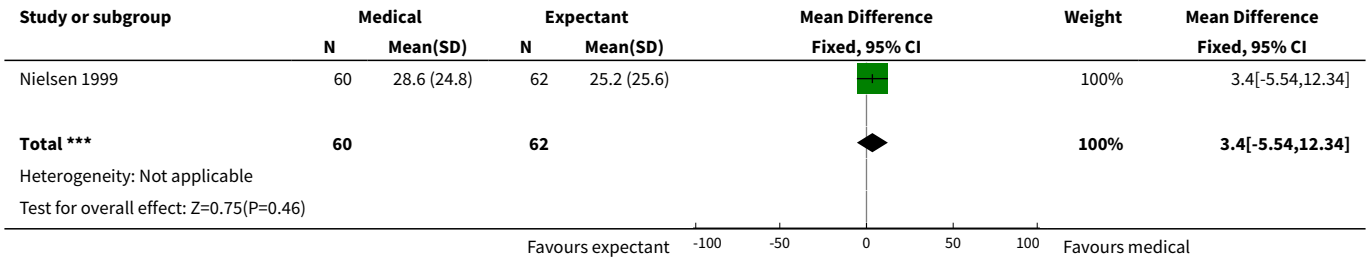
Analysis 17.4. Comparison 17 Oral misoprostol + mifepristone versus expectant management, Outcome 4 Pain.



Analysis 17.5. Comparison 17 Oral misoprostol + mifepristone versus expectant management, Outcome 5 Pelvic infection.



Analysis 17.6. Comparison 17 Oral misoprostol + mifepristone versus expectant management, Outcome 6 Woman's satisfaction with treatment (visual analogue scale day 14).



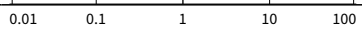
Comparison 18. Buccal misoprostol lower versus higher-dose regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage 13-23 weeks	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.58, 0.86]
1.1 Complete miscarriage < 1 day	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.89]
1.2 Complete miscarriage < 2 days	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.60, 0.96]
2 Nausea	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.28, 1.34]
2.1 Gestation 14-24 weeks	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.28, 1.34]
3 Vomiting	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.12, 0.76]
3.1 Gestation 14-24 weeks	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.12, 0.76]
4 Diarrhoea	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.19, 0.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Gestation 14-24 weeks	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.19, 0.82]
5 Pain	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.87, 1.06]
5.1 Gestation 14-24 weeks	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.87, 1.06]
6 Woman's satisfaction with treatment (satisfied or very satisfied)	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.17]
6.1 Gestation 14-24 weeks	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.17]

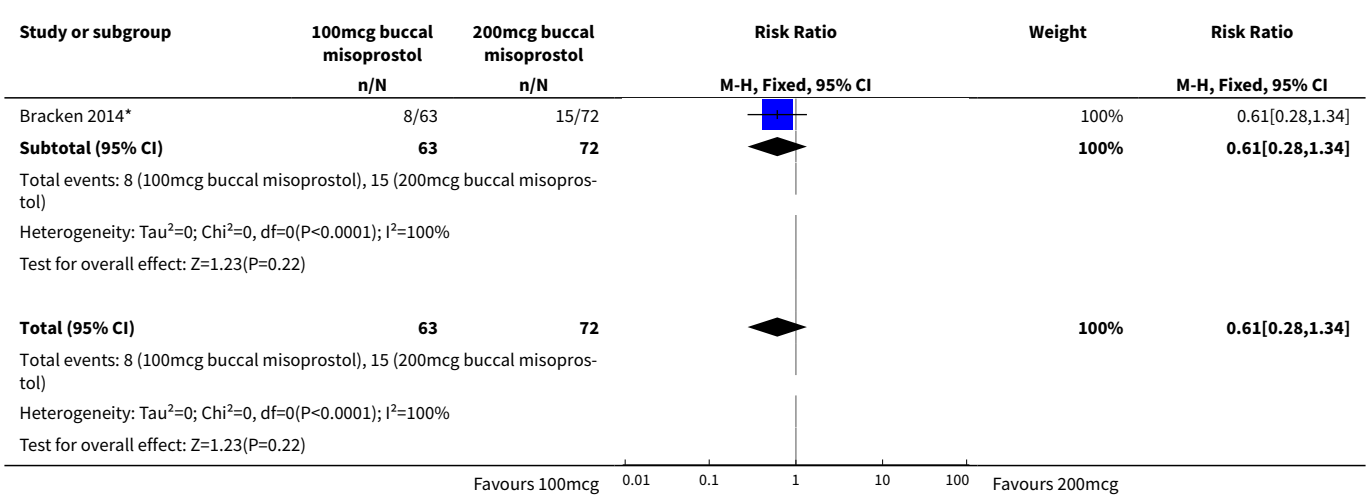
Analysis 18.1. Comparison 18 Buccal misoprostol lower versus higher-dose regimen, Outcome 1 Complete miscarriage 13-23 weeks.

Study or subgroup	100mcg buccal misoprostol n/N	200mcg buccal misoprostol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
18.1.1 Complete miscarriage < 1 day					
Bracken 2014*	27/63	48/72		45.71%	0.64[0.46,0.89]
Subtotal (95% CI)	**63**	**72**		**45.71%**	**0.64[0.46,0.89]**
Total events: 27 (100mcg buccal misoprostol), 48 (200mcg buccal misoprostol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.64(P=0.01)					
18.1.2 Complete miscarriage < 2 days					
Bracken 2014*	38/63	57/72		54.29%	0.76[0.6,0.96]
Subtotal (95% CI)	**63**	**72**		**54.29%**	**0.76[0.6,0.96]**
Total events: 38 (100mcg buccal misoprostol), 57 (200mcg buccal misoprostol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.29(P=0.02)					
Total (95% CI)	**126**	**144**		**100%**	**0.71[0.58,0.86]**
Total events: 65 (100mcg buccal misoprostol), 105 (200mcg buccal misoprostol)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.72$, df=1(P=0.4); $I^2=0\%$					
Test for overall effect: Z=3.49(P=0)					
Test for subgroup differences: $Chi^2=0.68$, df=1 (P=0.41), $I^2=0\%$					

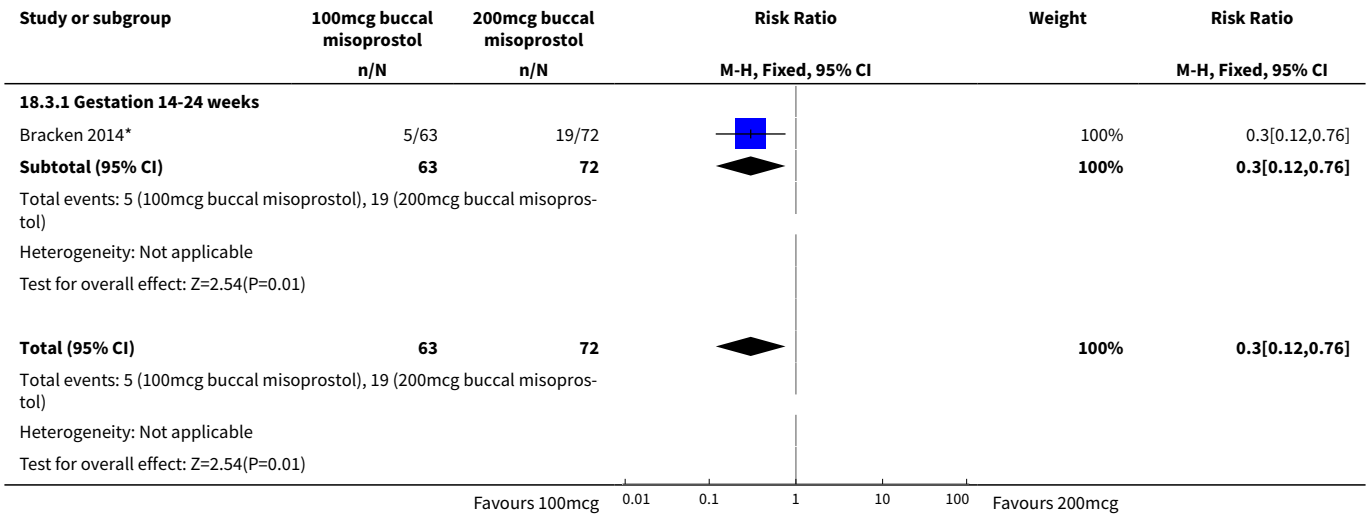


Analysis 18.2. Comparison 18 Buccal misoprostol lower versus higher-dose regimen, Outcome 2 Nausea.

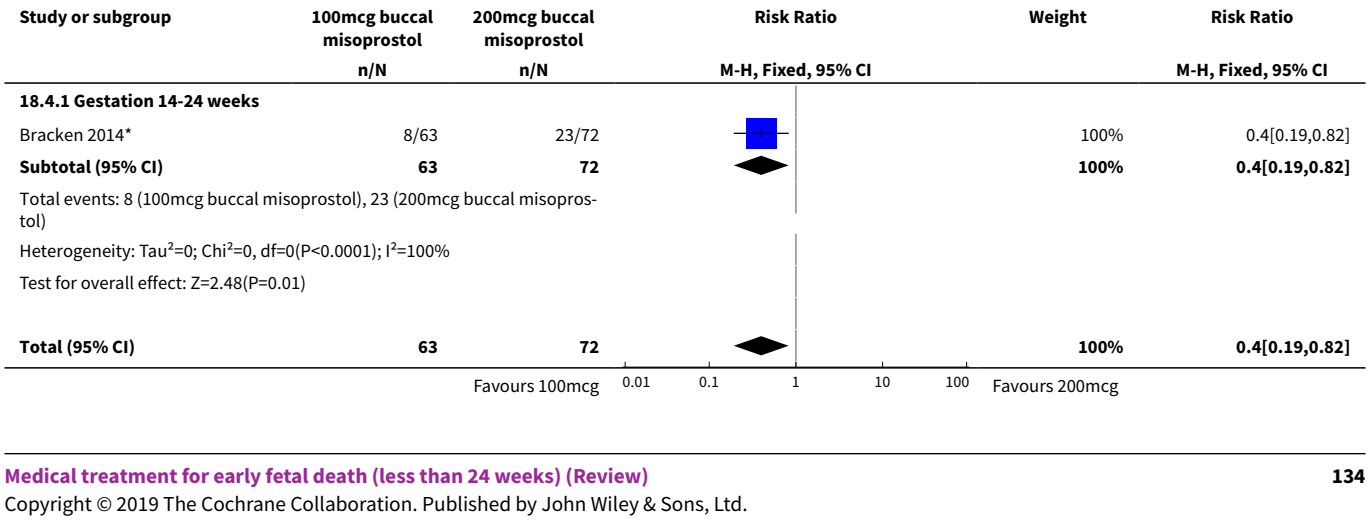
Study or subgroup	100mcg buccal misoprostol n/N	200mcg buccal misoprostol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
18.2.1 Gestation 14-24 weeks					



Analysis 18.3. Comparison 18 Buccal misoprostol lower versus higher-dose regimen, Outcome 3 Vomiting.



Analysis 18.4. Comparison 18 Buccal misoprostol lower versus higher-dose regimen, Outcome 4 Diarrhoea.



Study or subgroup	100mcg buccal misoprostol n/N	200mcg buccal misoprostol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 8 (100mcg buccal misoprostol), 23 (200mcg buccal misoprostol)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.48(P=0.01)					

Favours 100mcg 0.01 0.1 1 10 100 Favours 200mcg

Analysis 18.5. Comparison 18 Buccal misoprostol lower versus higher-dose regimen, Outcome 5 Pain.

Study or subgroup	100mcg buccal misoprostol n/N	200mcg buccal misoprostol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
18.5.1 Gestation 14-24 weeks					
Bracken 2014*	57/63	68/72		100%	0.96[0.87,1.06]
Subtotal (95% CI)	**63**	**72**		**100%**	**0.96[0.87,1.06]**
Total events: 57 (100mcg buccal misoprostol), 68 (200mcg buccal misoprostol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.86(P=0.39)					
Total (95% CI)	**63**	**72**		**100%**	**0.96[0.87,1.06]**
Total events: 57 (100mcg buccal misoprostol), 68 (200mcg buccal misoprostol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.86(P=0.39)					

Favours 100mcg 0.01 0.1 1 10 100 Favours 200mcg

Analysis 18.6. Comparison 18 Buccal misoprostol lower versus higher-dose regimen, Outcome 6 Woman's satisfaction with treatment (satisfied or very satisfied).

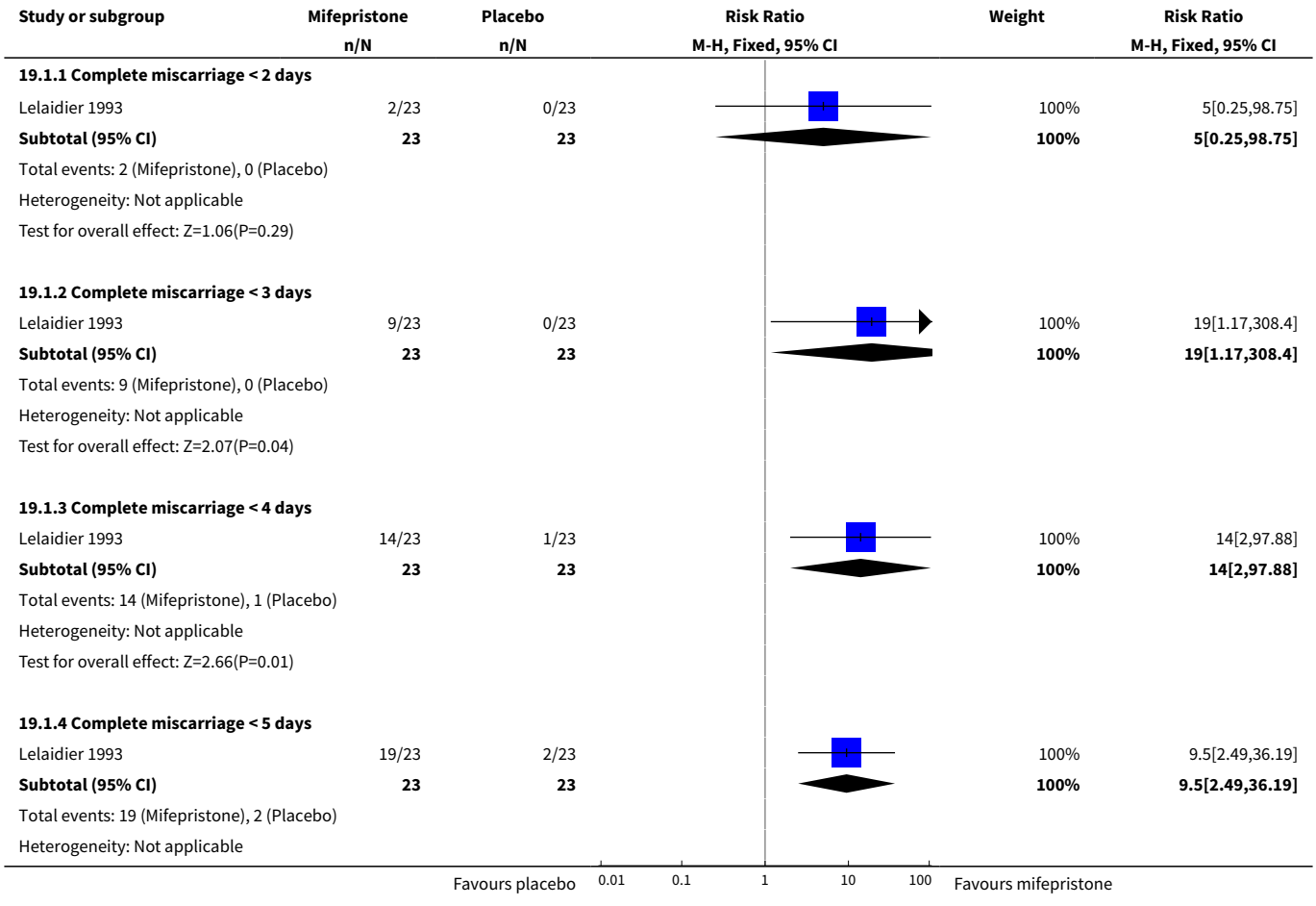
Study or subgroup	100mcg buccal misoprostol n/N	200mcg buccal misoprostol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
18.6.1 Gestation 14-24 weeks					
Bracken 2014*	45/63	54/72		100%	0.95[0.78,1.17]
Subtotal (95% CI)	**63**	**72**		**100%**	**0.95[0.78,1.17]**
Total events: 45 (100mcg buccal misoprostol), 54 (200mcg buccal misoprostol)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.47(P=0.64)					
Total (95% CI)	**63**	**72**		**100%**	**0.95[0.78,1.17]**
Total events: 45 (100mcg buccal misoprostol), 54 (200mcg buccal misoprostol)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.47(P=0.64)					

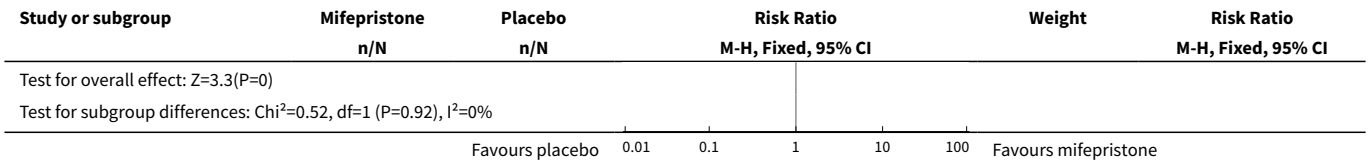
Favours 200mcg 0.01 0.1 1 10 100 Favours 100mcg

Comparison 19. Mifepristone versus placebo

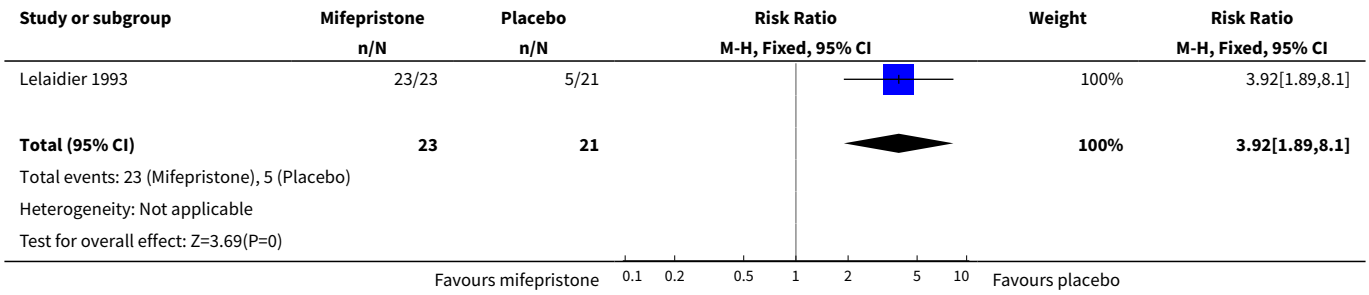
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Complete miscarriage < 2 days	1	46	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 98.75]
1.2 Complete miscarriage < 3 days	1	46	Risk Ratio (M-H, Fixed, 95% CI)	19.0 [1.17, 308.40]
1.3 Complete miscarriage < 4 days	1	46	Risk Ratio (M-H, Fixed, 95% CI)	14.0 [2.00, 97.88]
1.4 Complete miscarriage < 5 days	1	46	Risk Ratio (M-H, Fixed, 95% CI)	9.5 [2.49, 36.19]
2 Days of bleeding	1	44	Risk Ratio (M-H, Fixed, 95% CI)	3.92 [1.89, 8.10]
3 Pain	1	44	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [0.93, 5.17]

Analysis 19.1. Comparison 19 Mifepristone versus placebo, Outcome 1 Complete miscarriage.

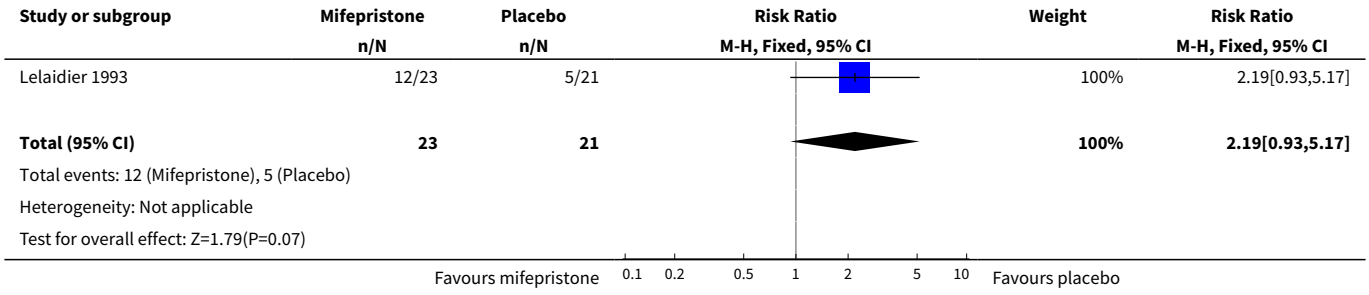




Analysis 19.2. Comparison 19 Mifepristone versus placebo, Outcome 2 Days of bleeding.



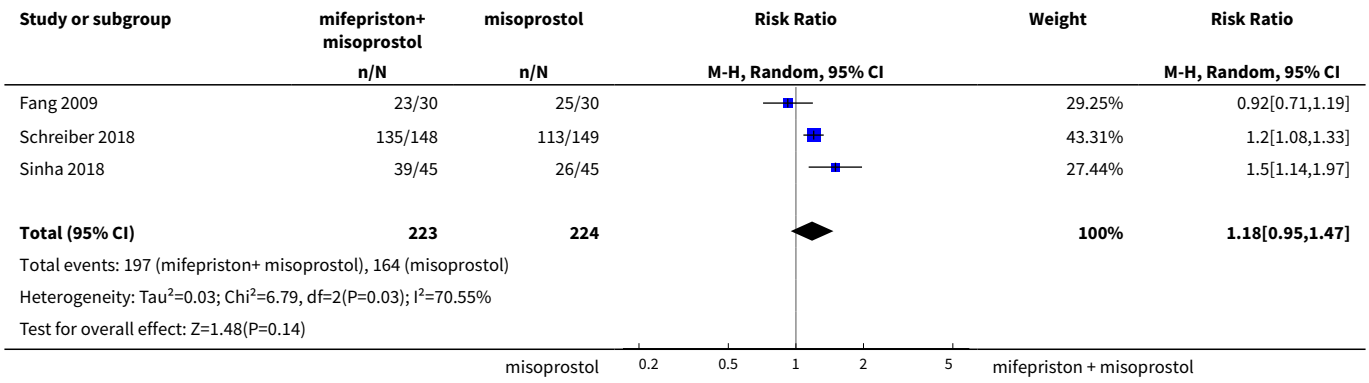
Analysis 19.3. Comparison 19 Mifepristone versus placebo, Outcome 3 Pain.



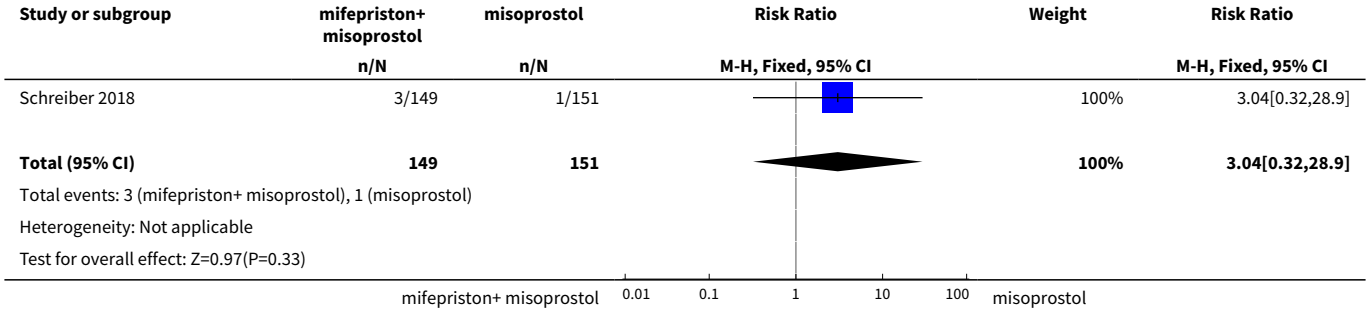
Comparison 20. Mifepristone + vaginal misoprostol versus vaginal misoprostol alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	3	447	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.95, 1.47]
2 Blood transfusion	1	300	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.32, 28.90]
3 Pelvic infection	1	300	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.14, 7.10]
4 nausea	1	300	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.76, 1.36]
5 Diarrhoea	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.66, 1.35]
6 Woman's satisfaction	2	135	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.06, 1.75]

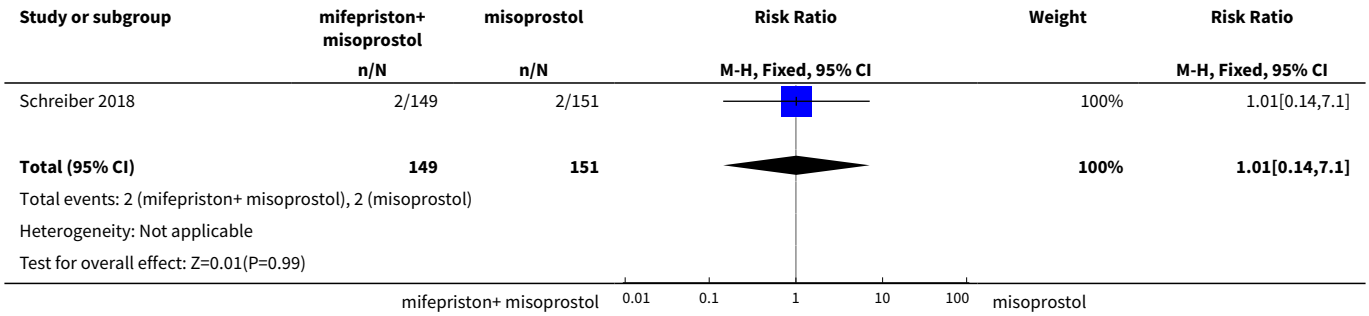
Analysis 20.1. Comparison 20 Mifepristone + vaginal misoprostol versus vaginal misoprostol alone, Outcome 1 Complete miscarriage.



Analysis 20.2. Comparison 20 Mifepristone + vaginal misoprostol versus vaginal misoprostol alone, Outcome 2 Blood transfusion.



Analysis 20.3. Comparison 20 Mifepristone + vaginal misoprostol versus vaginal misoprostol alone, Outcome 3 Pelvic infection.



Analysis 20.4. Comparison 20 Mifepristone + vaginal misoprostol versus vaginal misoprostol alone, Outcome 4 nausea.

Study or subgroup	mifepriston+ misoprostol n/N	misoprostol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schreiber 2018	56/149	56/151		100%	1.01[0.76,1.36]
Total (95% CI)	**149**	**151**		**100%**	**1.01[0.76,1.36]**
Total events: 56 (mifepriston+ misoprostol), 56 (misoprostol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.09(P=0.93)					

mifepriston+ misoprostol misoprostol

Analysis 20.5. Comparison 20 Mifepristone + vaginal misoprostol versus vaginal misoprostol alone, Outcome 5 Diarrhoea.

Study or subgroup	mifepriston+ misoprostol n/N	misoprostol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schreiber 2018	41/149	44/151		100%	0.94[0.66,1.35]
Total (95% CI)	**149**	**151**		**100%**	**0.94[0.66,1.35]**
Total events: 41 (mifepriston+ misoprostol), 44 (misoprostol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.31(P=0.76)					

misoprostol mifepriston+ misoprostol

Analysis 20.6. Comparison 20 Mifepristone + vaginal misoprostol versus vaginal misoprostol alone, Outcome 6 Woman's satisfaction.

Study or subgroup	mifepriston+ misoprostol n/N	misoprostol n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Fang 2009	16/30	7/15		15.22%	1.14[0.6,2.16]
Sinha 2018	38/45	27/45		84.78%	1.41[1.07,1.84]
Total (95% CI)	**75**	**60**		**100%**	**1.36[1.06,1.75]**
Total events: 54 (mifepriston+ misoprostol), 34 (misoprostol)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=2.45(P=0.01)					

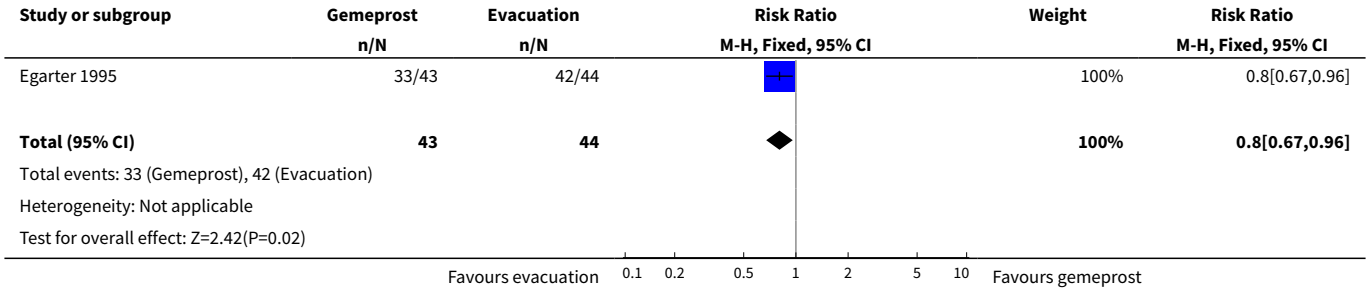
misoprostol mifepriston + misoprostol

Comparison 21. Vaginal gemeprost versus surgical evacuation of uterus

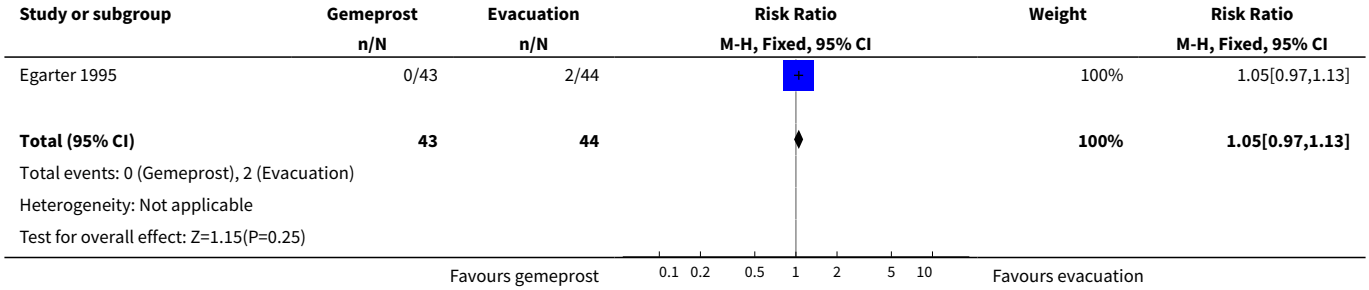
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.67, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Death or serious complications (uterine perforation)	1	87	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.97, 1.13]
3 Nausea	1	87	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.56, 5.68]

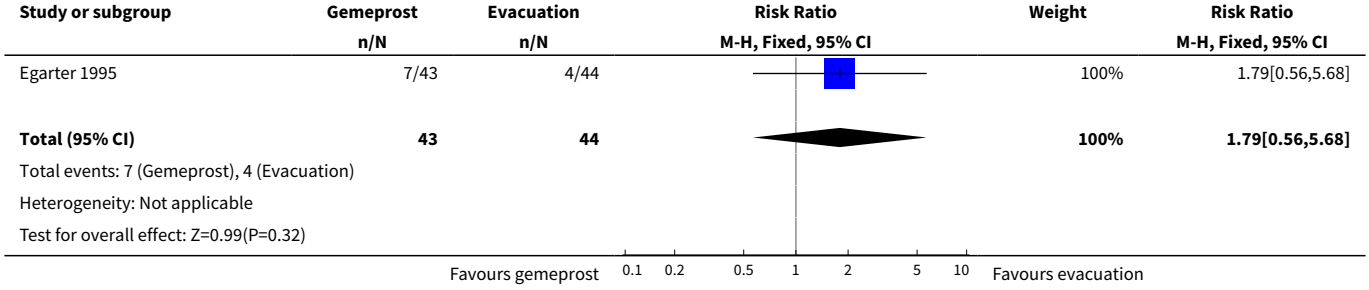
Analysis 21.1. Comparison 21 Vaginal gemeprost versus surgical evacuation of uterus, Outcome 1 Complete miscarriage.



Analysis 21.2. Comparison 21 Vaginal gemeprost versus surgical evacuation of uterus, Outcome 2 Death or serious complications (uterine perforation).



Analysis 21.3. Comparison 21 Vaginal gemeprost versus surgical evacuation of uterus, Outcome 3 Nausea.



Comparison 22. Misoprostol intravaginal extraamniotic versus vaginal misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	1	180	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.00, 1.22]
2 Nausea	1	180	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.33, 1.85]
3 Vomiting	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.05, 1.14]
4 Diarrhoea	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.11]
5 Pain (use of analgesics)	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.16, 0.58]
6 Time to expulsion	1	180	Mean Difference (IV, Fixed, 95% CI)	-4.81 [-5.66, -3.96]

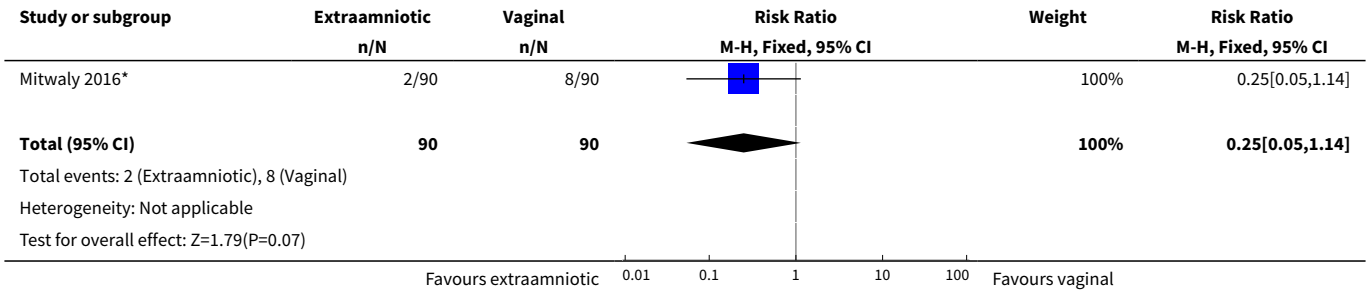
Analysis 22.1. Comparison 22 Misoprostol intravaginal extraamniotic versus vaginal misoprostol, Outcome 1 Complete miscarriage.

Study or subgroup	Extraamniotic n/N	Vaginal n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mitwaly 2016*	85/90	77/90		100%	1.1[1,1.22]
Total (95% CI)	**90**	**90**		**100%**	**1.1[1,1.22]**
Total events: 85 (Extraamniotic), 77 (Vaginal)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.97(P=0.05)					

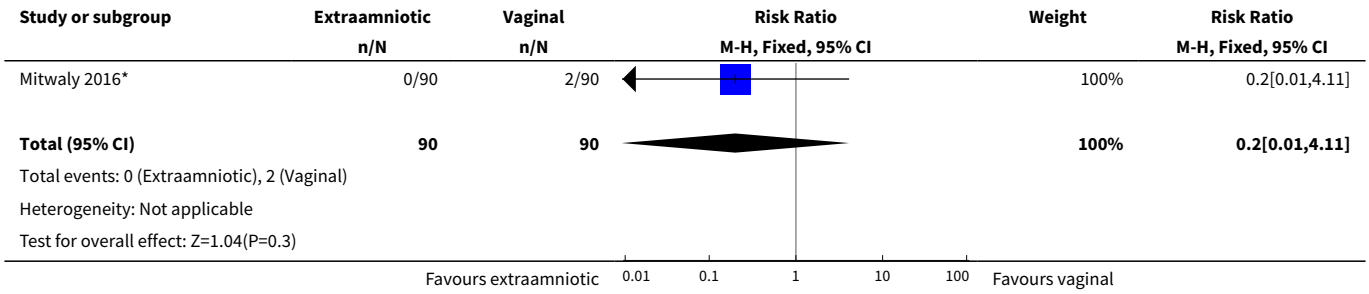
Analysis 22.2. Comparison 22 Misoprostol intravaginal extraamniotic versus vaginal misoprostol, Outcome 2 Nausea.

Study or subgroup	Extraamniotic n/N	Vaginal n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mitwaly 2016*	2/90	34/90		100%	1.57[1.33,1.85]
Total (95% CI)	**90**	**90**		**100%**	**1.57[1.33,1.85]**
Total events: 2 (Extraamniotic), 34 (Vaginal)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.4(P<0.0001)					

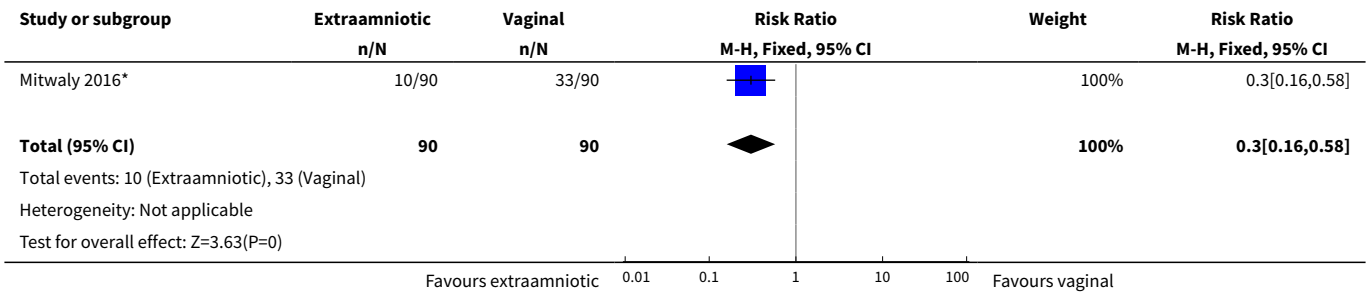
Analysis 22.3. Comparison 22 Misoprostol intravaginal extraamniotic versus vaginal misoprostol, Outcome 3 Vomiting.



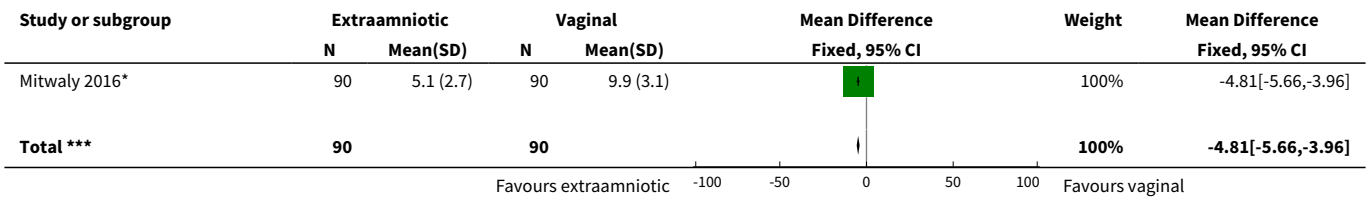
Analysis 22.4. Comparison 22 Misoprostol intravaginal extraamniotic versus vaginal misoprostol, Outcome 4 Diarrhoea.

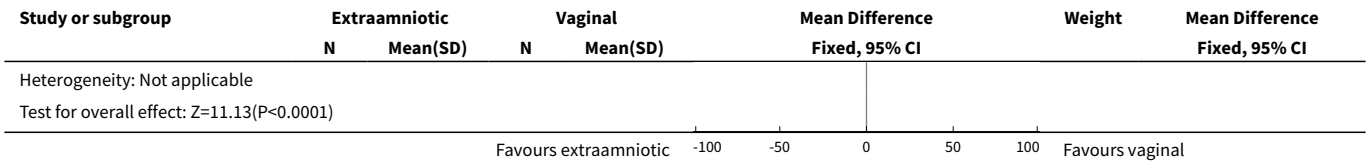


Analysis 22.5. Comparison 22 Misoprostol intravaginal extraamniotic versus vaginal misoprostol, Outcome 5 Pain (use of analgesics).



Analysis 22.6. Comparison 22 Misoprostol intravaginal extraamniotic versus vaginal misoprostol, Outcome 6 Time to expulsion.

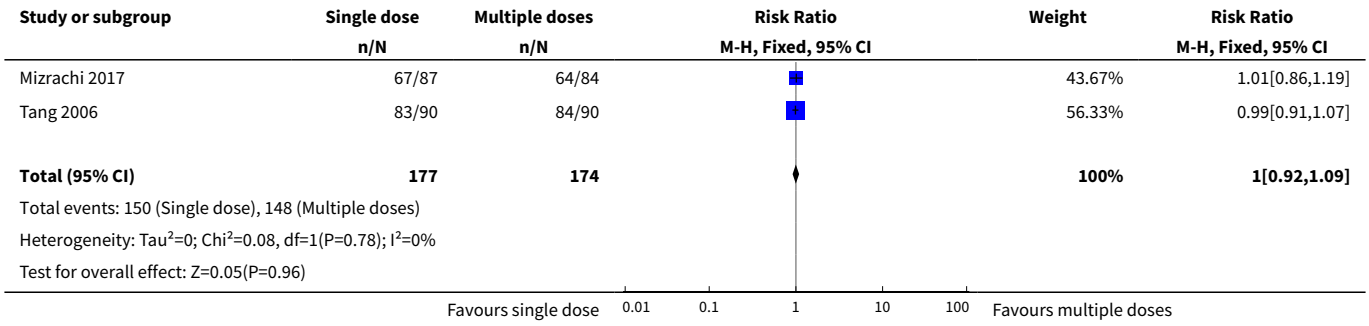




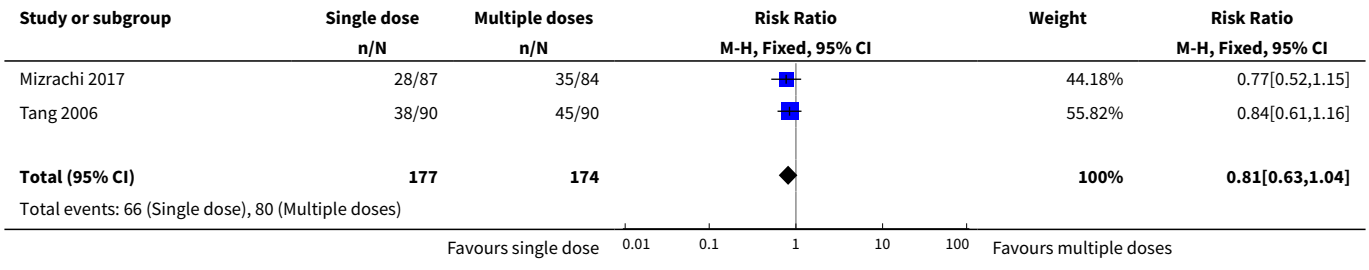
Comparison 23. Vaginal misoprostol with versus without extended course

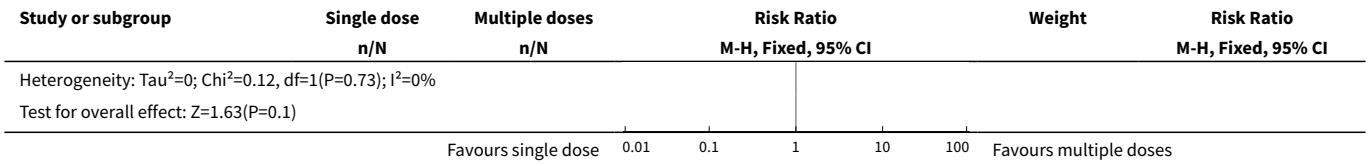
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete miscarriage	2	351	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.92, 1.09]
2 Nausea	2	351	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.63, 1.04]
3 Vomiting	2	351	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.68, 2.06]
4 Diarrhoea	2	351	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.82, 1.22]
5 Pain (use of analgesics)	1	171	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.71, 1.00]
6 Woman's satisfaction with treatment	1	171	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.84, 1.22]

Analysis 23.1. Comparison 23 Vaginal misoprostol with versus without extended course, Outcome 1 Complete miscarriage.

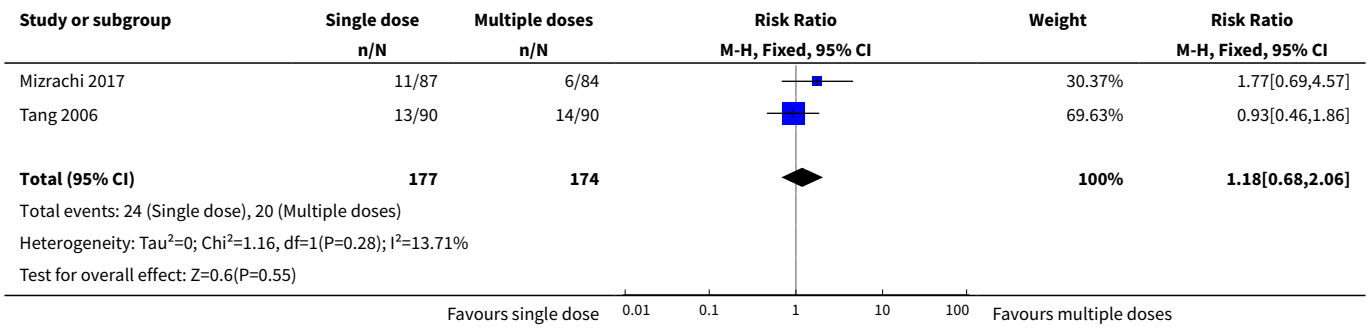


Analysis 23.2. Comparison 23 Vaginal misoprostol with versus without extended course, Outcome 2 Nausea.

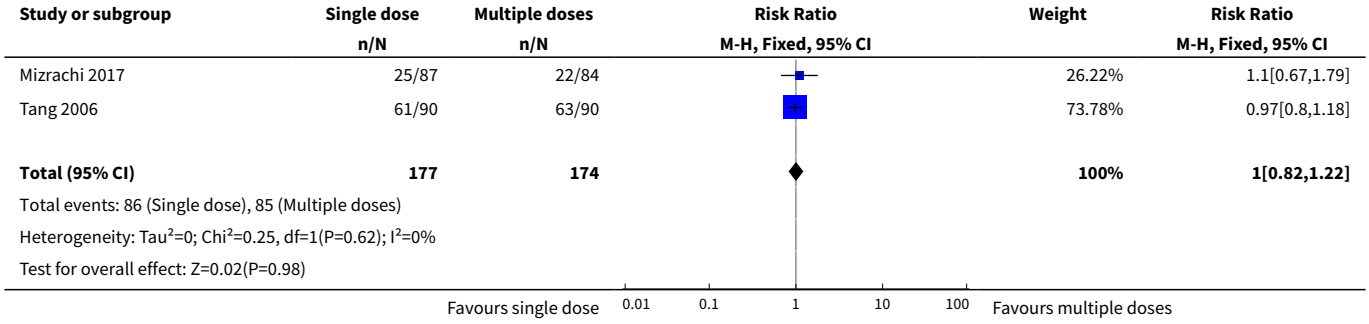




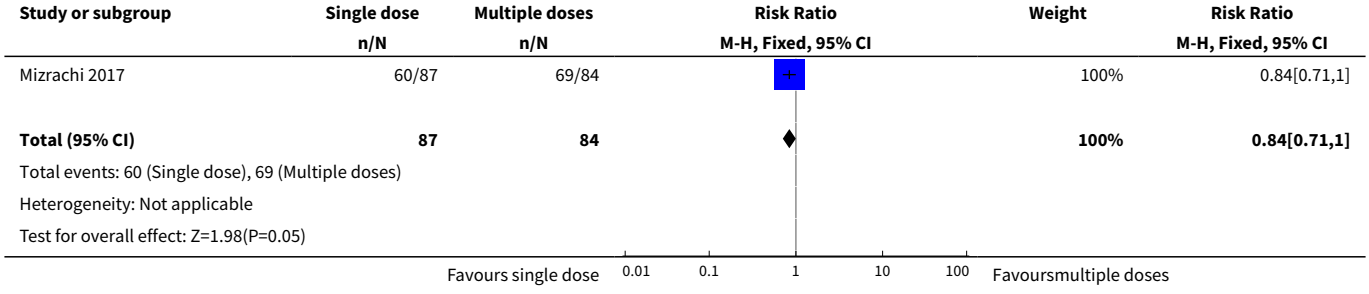
Analysis 23.3. Comparison 23 Vaginal misoprostol with versus without extended course, Outcome 3 Vomiting.



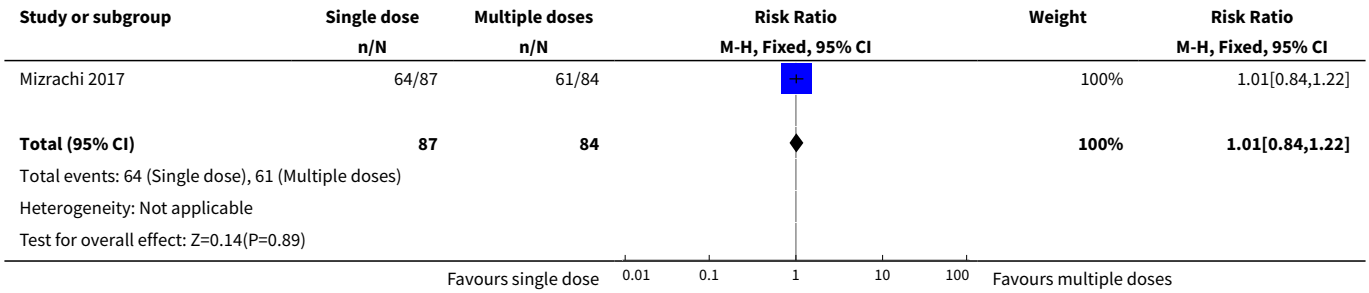
Analysis 23.4. Comparison 23 Vaginal misoprostol with versus without extended course, Outcome 4 Diarrhoea.



Analysis 23.5. Comparison 23 Vaginal misoprostol with versus without extended course, Outcome 5 Pain (use of analgesics).



Analysis 23.6. Comparison 23 Vaginal misoprostol with versus without extended course, Outcome 6 Woman's satisfaction with treatment.



APPENDICES

Appendix 1. Search terms for ClinicalTrials.gov and ICTRP

Each line was run separately

fetal death

anembryonic pregnancy

fetal demise

pregnancy loss

non viable pregnancy

WHAT'S NEW

Date	Event	Description
24 October 2018	New citation required but conclusions have not changed	This update has added 21 new studies. Two studies previously included have now been excluded (Fadalla 2004*; Heard 2002). Ten new comparisons have been added. The review now includes a total of 23 comparisons including a wide variety of different interventions, mainly consisting of single studies. The available evidence from randomised control trials still supports the use of vaginal misoprostol.
24 October 2018	New search has been performed	Search updated. 'Summary of findings' tables incorporated.

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 3, 2006

Date	Event	Description
8 August 2012	Amended	Search updated. One hundred reports added to Studies awaiting classification.
18 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Marike Lemmers: screening for in/exclusion, data extraction, data analyses, quality of evidence assessment, completing first draft, and further revisions of the updated review.

Marianne Verschoor: review update protocol development, screening for in/exclusion, data extraction, data entry, analyses, quality of evidence assessment, assisting first draft of the updated review.

Bobae Kim: data extraction, data entry, quality of evidence assessment, revisions to first draft of the updated review.

Martha Hickey: original protocol development and revisions to the first draft of the original review.

Juan Vazquez: original protocol development and revisions to first draft of the original review.

Ben Willem Mol: supervision of review update protocol development, supervision of data extractions, data entry and analyses, revisions to first draft of the updated review.

Jim Neilson: supervision of original protocol development; completion of first draft of original review. Supervision of total process of preparing the updated review.

DECLARATIONS OF INTEREST

Marike Lemmers: for previous work (the MisoREST trial), which focuses on miscarriage treatment, my institution (AMC) received a ZonMW grant. ZonMW is a Dutch governmental organization for Health Research and Development.

Marianne AC Verschoor: my institution linked received a ZonMW grant for the MisoREST study.

Bobae Veronica Kim: none known.

Martha Hickey: none known.

Juan C Vazquez: none known.

Ben Willem J Mol: my institution and I have received payment for consultancy from ObsEva Geneva. I have received payment for review preparation from Eur J Obste Gynaecol and I have received travel/accommodation/meeting expenses for various non-commercial scientific meetings.

James P Neilson: none known.

SOURCES OF SUPPORT

Internal sources

- America Arias Hospital, Havana, Cuba.
- The University of Liverpool, UK.
- Academic Medical Centre, Amsterdam, Netherlands.

External sources

- HRP/WHO, Geneva, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for this review aimed to include both trials for treatment of both ultrasound-diagnosed, non-viable pregnancies and incomplete miscarriage. For the reasons described in the review, two separate reviews now address these topics - thus, the change in title from '*Medical management for miscarriage*' to '*Medical treatment for early fetal death (less than 24 weeks)*'.

In this update, the evidence has been assessed for quality using the GRADE approach and 'Summary of findings' tables have been incorporated.

Several subgroup analyses that were not prespecified have been performed because there were subgroups of clinical interest. These included the following.

For comparison 1: vaginal misoprostol versus placebo; primary outcome complete miscarriage:

1. complete miscarriage less than one day;
2. complete miscarriage less than two days;
3. complete miscarriage less than seven days.

For comparison 6: vaginal misoprostol wet versus dry preparations: primary outcome complete miscarriage:

1. complete miscarriage less than three days;
2. complete miscarriage less than eight days;
3. complete miscarriage less than 15 days;
4. complete miscarriage less than 30 days.

For comparison 8: vaginal misoprostol plus laminaria tents versus vaginal misoprostol alone: primary outcome complete miscarriage:

1. complete miscarriage less than one day;
2. complete miscarriage less than two days.

For comparison 18: buccal misoprostol lower versus higher regimen: primary outcome complete miscarriage 13 to 23 weeks:

1. complete miscarriage less than one day;
2. complete miscarriage less than two days.

For comparison 19: mifepristone versus placebo: primary outcome complete miscarriage:

1. complete miscarriage less than two days;
2. complete miscarriage less than three days;
3. complete miscarriage less than four days;
4. complete miscarriage less than five days.

In the protocol "pain relief" was determined as outcome. However, various articles had different ways to assess pain relief or pain. We therefore added an extra definition to this outcome to further specify.

in the 2018 update, we added in an additional search of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports.

INDEX TERMS

Medical Subject Headings (MeSH)

*Fetal Death; *Mifepristone [administration & dosage]; *Misoprostol [administration & dosage]; *Oxytocics [administration & dosage]; Delivery, Obstetric; Pregnancy Trimester, First; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy