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

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TABLE OF CONTENTS

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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 before 14 weeks has traditionally been surgical but medical treatments may be effective, safe, and acceptable, as may be waiting for spontaneous miscarriage.

Objectives
To assess the effectiveness, safety and acceptability of any medical treatment for early pregnancy failure (anembryonic pregnancies or embryonic and fetal deaths before 24 weeks).

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group Trials Register (30 November 2005).

Selection criteria
Randomised trials comparing medical treatment with another treatment (e.g. surgical evacuation), or placebo, or no treatment for early pregnancy failure. Quasi-random studies were excluded.

Data collection and analysis
Data were extracted unblinded.

Main results
Twenty four studies (1888 women) were included.

Vaginal misoprostol hastens miscarriage (complete or incomplete) when compared with placebo: e.g. miscarriage less than 24 hours (two trials, 138 women, relative risk (RR) 4.73, 95% confidence interval (CI) 2.70 to 8.28), with less need for uterine curettage (two trials, 104 women, RR 0.40, 95% CI 0.26 to 0.60) and no significant increase in nausea or diarrhoea. Lower-dose regimens of vaginal misoprostol tend to be less effective in producing miscarriage (three trials, 247 women, RR 0.85, 95% CI 0.72 to 1.00) with similar incidence of nausea. There seems no clear advantage to administering a 'wet' preparation of vaginal misoprostol or of adding methotrexate, or of using laminaria tents after 14 weeks. Vaginal misoprostol is more effective than vaginal prostaglandin E in avoiding surgical evacuation. Oral misoprostol was less effective than vaginal misoprostol in producing complete miscarriage (two trials, 218 women, RR 0.90, 95% CI 0.82 to 0.99). Sublingual misoprostol had equivalent efficacy to vaginal misoprostol in inducing complete miscarriage but was associated with more frequent diarrhoea. The two trials of mifepristone treatment generated conflicting results. There was no statistically significant difference between vaginal misoprostol and gemeprost in the induction of miscarriage for fetal death after 13 weeks.

Authors' conclusions
Available evidence from randomised trials supports the use of vaginal misoprostol as a medical treatment to terminate non-viable pregnancies before 24 weeks. Further research is required to assess effectiveness and safety, optimal route of administration and dose. Conflicting findings about the value of mifepristone need to be resolved by additional study.

PLAIN LANGUAGE SUMMARY

Medical treatments for inevitable miscarriage

Pregnancies that miscarry can sometimes be identified earlier at an ultrasound scan if the loss is due to the baby having died or no baby having developed. In the past, treatment before 14 weeks has usually been by surgery (D&C) but drugs have now been developed which may be helpful, or waiting for the miscarriage to happen may be a better alternative. The review of trials assessed various potential drug treatments using different routes and different doses, compared with waiting for the miscarriage. This review identified 24 studies involving 1888 women of less than 24 weeks gestation, where the baby had died in the uterus or the baby had not formed in the uterus. Most studies were of good quality. Vaginal misoprostol brought forward the time of the miscarriage, but the studies were too small to adequately assess potential adverse effects, including future fertility. Oral misoprostol seemed less effective than the vaginal route, and women took more sick-leave with the oral drugs. Some women may wish to hasten an inevitable miscarriage, and others may not. It appears that both forms of care can be available to women. Women who are breastfeeding an older baby may prefer to wait rather than have drug treatment. 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.

BACKGROUND

The incidence of clinically obvious miscarriage is considered to be between 10% and 15% of all pregnancies, although the real incidence may be considerably higher (Grudzinskas 1995; Howie 1995; Simpson 1991).

The widespread use of ultrasound in early pregnancy for either specific reasons (for example, vaginal bleeding) or as a routine examination (Neilson 1998) reveals 'non-viable pregnancies' destined inevitably to miscarry in due course. These are termed 'anembryonic pregnancies' (formerly called 'blighted ova') if no embryo has developed within the gestation sac, or 'missed abortions' if an embryo or fetus is present, but is dead.

The 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 will assess trials of medical treatments after miscarriage has occurred (Vazquez 2000). A further review compares expectant management with surgical treatment for miscarriage (Nanda 2002).

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.

Various types of medical treatment could be suitable as alternatives to surgical treatment: misoprostol is a prostaglandin E1 analogue, marketed for the prevention and treatment of peptic ulcers. Recognized as a potent method for terminating unwanted viable pregnancies (Costa 1993; Norman 1991), it is cheap, stable at room temperature and has few systemic effects, although vomiting, diarrhoea, hypertension and even potential teratogenicity when misoprostol fails to induce abortion have been reported (Fonseca 1991). Misoprostol has been shown to be an effective myometrial stimulant of the pregnant uterus, selectively binding to EP-2/EP-3 prostanoid receptors (Senior 1993). It is rapidly absorbed orally and vaginally. Vaginally absorbed serum levels are more prolonged and vaginal misoprostol may have locally mediated effects (Zieman 1997).

Misoprostol could be especially useful in developing countries, where transport and storage facilities are inadequate and the availability of uterotonic agents and blood is limited. Its use in obstetrics and gynecology has been explored, especially to induce first and second trimester abortion (Ashok 1998; Bugalho 1996), for the induction of labour (Alfirevic 2001; Hofmeyr 2003) and for the prevention of postpartum haemorrhage (Gulmezoglu 2004) despite the fact that it has not been registered for such use.

Other uterotonic drugs that could have a role would include ergometrine, oxytocin, and prostaglandin F2alpha.

The progesterone antagonist, mifepristone, is of value in terminating early unwanted pregnancies and may be of use in non-viable pregnancies and spontaneous miscarriage (Baulieu 1986; Kovacs 1984), alone or in combination with prostaglandin (Cameron 1986).

Methotrexate may be helpful in the medical treatment of ectopic pregnancy and might therefore have a place in the treatment of intrauterine non-viable pregnancies as well. It has also been used for the early termination of unwanted pregnancy, followed by a uterotonic agent such as misoprostol.

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.

OBJECTIVES

To assess, from clinical trials, the effectiveness and safety of different medical treatments for the termination of non-viable pregnancies, with reference to death or serious complications, additional surgical evacuation, blood transfusion, haemorrhage, blood loss, anaemia, days of bleeding, pain relief, pelvic infection, cervical damage, duration of stay in hospital, psychological effects, subsequent fertility, women's satisfaction and costs.

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; random allocation to treatment and comparison groups; reasonable measures to ensure allocation concealment; and violations of allocated management not sufficient to materially affect outcomes. Quasi-random studies were excluded.

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. Subgroup analyses to be performed, if possible, for women at less than 14 weeks, and those between 14 and 23 weeks estimated gestational age.

Types of intervention

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 reported.

Primary outcomes

(1) Complete miscarriage (i.e. no pregnancy tissues remaining in uterus - based on clinical findings at surgery and/or ultrasound examination after a specific period).
(2) Death or serious complications (e.g. uterine rupture, uterine perforation, hysterectomy, organ failure, intensive care unit admission).

Secondary outcomes

(1) Additional surgical evacuation
(2) Blood transfusion
(3) Haemorrhage
(4) Blood loss
(5) Anemia
(6) Days of bleeding
(7) Pain relief
(8) Pelvic infection
(9) Cervical damage
(10) Digestive disorders (nausea or vomiting or diarrhoea)
(11) Hypertensive disorders
(12) Duration of stay in hospital
(13) Psychological effects
(14) Subsequent fertility
(15) Woman's satisfaction/acceptability of method
(16) Costs

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (30 November 2005).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
(1) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
(2) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator

searches the register for each review using these codes rather than keywords.

We did not apply any language restrictions.

METHODS OF THE REVIEW

We assessed all potential trials for eligibility according to the criteria specified in the protocol. A single author extracted data from each publication and co-authors checked the data. We resolved any discrepancies by discussion. 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 all collected. An intention-to-treat analysis was performed where possible. Any information on completeness of follow up was collected as well.

Trials were assessed for methodological quality using the standard Cochrane criteria of adequacy of allocation concealment:
(A) adequate;
(B) unclear;
(C) inadequate;
(D) allocation concealment was not used.

We collected information on blinding of outcome assessment and loss to follow up.

Separate comparisons were made of different drug regimens, grouped where appropriate by number of doses given and the route of administration. Summary relative risks were calculated using a fixed-effect model (providing there was no significant heterogeneity between trials - defined as I squared greater than 50%). Because of the small number of trials and comparisons, it was impossible to perform sensitivity analysis using trial quality (A versus B, C, D).

DESCRIPTION OF STUDIES

This review has included 24 studies comparing vaginal misoprostol to expectant management (Bagratee 2004), placebo (Herabutya 1997; Kovavisarach 2002; Lister 2005; Wood 2002), surgical evacuation (Demetroulis 2001; Graziosi 2004; Muffley 2002), oral or sublingual misoprostol (Creinin 1997; Ngoc 2004; Tang 2003), other types of vaginal or intracervical prostaglandin preparation (Al Inizi 2003; Eng 1997*; Fadalla 2004*; Kara 1999*); different doses (Heard 2002; Kovavisarach 2005; Niromanesh 2005*) and preparations (Gilles 2004) of vaginal misoprostol; the addition to vaginal misoprostol of methotrexate (Autry 1999) or laminaria tents (Jain 1996*); mifepristone versus placebo (Lelaidier 1993); mifepristone plus oral misoprostol versus expectant management (Nielsen 1999), 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.

Five of the 24 included studies addressed medical treatment of non-viable pregnancies after 14 weeks (Eng 1997*; Fadalla 2004*; Jain 1996*; Kara 1999*; Niromanesh 2005*). These are labelled with an asterisk for ease of interpretation.

There are additional trials that have included data on women with both non-viable pregnancies and incomplete miscarriages (for example, Ngai 2001). If these can be separated by the researchers, these data may be included in the future.

METHODOLOGICAL QUALITY

Thirteen studies used robust methods of allocation concealment (Autry 1999; Bagratee 2004; Creinin 1997; Demetroulis 2001; Gilles 2004; Graziosi 2004; Kovavisarach 2005; Lelaidier 1993; Lister 2005; Muffley 2002; Ngoc 2004; Tang 2003; Wood 2002). Nine reports failed to describe the process of randomisation (Al Inizi 2003; Egarter 1995; Fadalla 2004*; Herabutya 1997; Jain 1996*; Kara 1999*; Kovavisarach 2002; Nielsen 1999; Niromanesh 2005*). One study has been reported only in abstract - without randomisation details (Heard 2002). In one study, allocation was based on picking an un-numbered envelope from a pack - a method that is recognised to be less robust (Eng 1997*).

In most trials, analysis by intention-to-treat was performed.

It was not possible to blind the physicians to the method of treatment in some studies - if this involved surgical evacuation of the uterus, alternative routes of drug administration (oral versus vaginal) or a policy of expectant management. It is, however, possible to blind the evaluator who assessed complications during the follow-up visit but no study made mention of this.

There was variation between studies in the timing of scheduled follow-up visits.

RESULTS

Twenty four studies, with a total of 1888 women, were included. Nineteen of the studies addressed termination of non-viable pregnancies before 14 weeks.

Treatment with vaginal misoprostol hastens miscarriage (passage of products of conception, whether complete or incomplete) when compared with placebo: miscarriage less than 24 hours (two trials,

138 women, relative risk (RR) 4.73, 95% confidence interval (CI) 2.70 to 8.28); miscarriage less than 48 hours (two (other) trials, 84 women, RR 5.74, 95% CI 2.70 to 12.19); complete miscarriage without need for surgical intervention at seven days (one trial, 83 women, RR 2.99, 95% CI 1.80 to 4.99). There was less need for uterine curettage (two trials, 104 women, RR 0.40, 95% CI 0.26 to 0.60) and no statistically significant increase in adverse effects: nausea (two trials, 88 women, RR 1.38, 95% CI 0.43 to 4.40), diarrhoea (two trials, 88 women, RR 2.21, 95% CI 0.35 to 14.06). One study showed a reduction in costs associated with a strategy of starting treatment with misoprostol, compared to immediate curettage (mean difference EUR192, 95% CI 33 to 351), no obvious difference in subsequent fertility, and similar numbers 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%).

Consistent with these observations, treatment with vaginal misoprostol decreases the need for surgical evacuation of the uterus when compared with a policy of arranging immediate surgical evacuation (three trials, 254 women, RR 0.42, 95% CI 0.34 to 0.52) at a cost of more nausea (one trial, 154 women, RR 21.85, 95% CI 1.31 to 364.37) and diarrhoea (one trial, 154 women, RR 40.85, 95% CI 2.52 to 662.57).

Vaginal misoprostol has been administered in doses of 400 mcg, 600 mcg, and 800 mcg in trials: lower-dose regimens tend to be less effective in producing miscarriage (three trials, 247 women, RR 0.85, 95% CI 0.72 to 1.00) with similar incidence of nausea (two trials, 214 women, RR 0.67, 95% CI 0.31 to 1.41). There seems no clear advantage to administering a 'wet' preparation of vaginal misoprostol compared to a 'dry' preparation: miscarriage less than three days (one trial, 80 women, RR 1.14, 95% CI 0.85 to 1.54). Adding methotrexate treatment to vaginal misoprostol has not been demonstrated to be advantageous in the single small trial to address this: miscarriage not complete after treatment (21 women, RR 0.26, 95% CI 0.01 to 5.65). Nor are laminaria tests proven useful adjuncts to vaginal misoprostol during the second trimester: complete miscarriage less than 24 hours (one trial, 38 women, RR 0.90, 95% CI 0.65 to 1.25), less than 48 hours (one trial, 38 women, RR 1.07, 95% CI 0.88 to 1.29). Vaginal misoprostol was more effective than vaginal prostaglandin E in avoiding surgical evacuation (one trial, 80 women, RR 0.39, 95% CI 0.21 to 0.72) and effecting complete miscarriage in the second trimester (one trial, 65 women, RR 1.44, 95% CI 1.06 to 1.96).

Overall, oral misoprostol was found to be less effective than vaginal misoprostol in producing complete miscarriage (two trials, 218 women, RR 0.90, 95% CI 0.82 to 0.99) but this difference was seen only with the 400 mcg oral dose (one trial, 20 women, RR 0.29, 95% CI 0.10 to 0.79) and not the 800 mcg oral dose (one trial, 198 women, RR 0.96, 95% CI 0.88 to 1.05). There was less vomiting with the oral regimen (one trial, 190 women, RR 0.29, 95% CI 0.10 to 0.84) but similar incidence of diarrhoea (two trials, 210 women, RR 1.05, 95% CI 0.67 to 1.66). There were high (and similar) levels of satisfaction with treatment (one trial, 198 women, RR 0.96, 95% CI 0.86 to 1.06). Oral misoprostol was slower than vaginal misoprostol in effecting miscarriage in a single trial of women with second trimester fetal death (weighted mean difference 4.10 hours, 95% CI 2.64 to 5.56).

Sublingual misoprostol had equivalent efficacy to vaginal misoprostol in inducing complete miscarriage (one trial, 80 women, RR 1.00, 95% CI 0.85 to 1.18) but was associated with more frequent diarrhoea (RR 2.65, 95% CI 1.48 to 4.38) but not other side-effects.

The two trials of mifepristone treatment generated conflicting results. One study found mifepristone to be much more effective than placebo: miscarriage complete by day five after treatment (46 women, RR 9.50, 95% CI 2.49 to 36.19). The other study compared treatment with mifepristone plus oral misoprostol with a policy of expectant management (no treatment); there was no statistically significant difference in complete miscarriage by day five (122 women, RR 1.08, 95% CI 0.90 to 1.30).

There was no statistically significant difference between vaginal misoprostol and gemeprost in the induction of miscarriage less than 24 hours for fetal death after 13 weeks (one trial, 50 women, RR 1.24, 95% CI 0.90 to 1.70).

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).

DISCUSSION

The large majority of included trials (21/24) addressed the use of misoprostol (mainly by vaginal administration). 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, and thus potentially especially useful in developing countries, where transport and storage facilities are inadequate and the availability of uterotonic agents and blood is limited. However, ultrasound imaging is needed to diagnose non-viable pregnancies and equipment is sparse in many developing countries. The reproductive use of misoprostol is considered in other Cochrane reviews, for indications that include termination of unwanted pregnancies (Kulier 2004; Say 2002), induction of labour (Alfirevic 2001; Hofmeyr 2003; Muzonzini 2004) and prevention and treatment of postpartum haemorrhage (Gulmezoglu 2004; Mousa 2003).

AUTHORS' CONCLUSIONS

Implications for practice

Available evidence from randomised trials supports the use of vaginal misoprostol as one possible option for the treatment of non-viable pregnancies before 24 weeks.

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 is required to assess the effectiveness, safety and side-effects of misoprostol, including optimal route of administration and dose. Conflicting findings about the value of mifepristone need to be resolved by additional study. Women's views about the acceptability of medical treatment, surgical treatment and expectant management should be integral to future research protocols, as should economic assessments. Long-term outcome, notably subsequent fertility, deserves further study in appropriately powered randomised controlled studies.

POTENTIAL CONFLICT OF INTEREST

None known.

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**Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Al Inizi 2003**
Methods	'Random allocation'. Details unknown.
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) versus dinoprostone (PGE2) vaginal tablets repeated 6 hourly intervals to maximum of 36 mg (n = 33).
Outcomes	Complete miscarriage/need for surgical evacuation.
Notes	Authors contacted.
Allocation concealment	B – Unclear

Study	**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 enrollment in the study. Intention to treat analysis.

Characteristics of included studies (*Continued*)

Participants	21 women diagnosed with a non-viable first trimester intrauterine pregnancy up to 49 days gestation. Evidence of non-viability included one of the following findings on TVS: 1) mean gestational sac diameter greater than 18 mm and no embryonic pole; 2) embryonic pole 5-10 mm without cardiac activity; 3) intrauterine gestational sac with abnormal hCG titers. 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) hemoglobin of 9 g/dl or greater; 5) platelet count of 100,000/mcl 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/m2 body surface area (day 1) followed two days later (day 3) by vaginal misoprostol 800 mcg (by vaginal placement of four 200 mcg-tablets of misoprostol). If the gestational sac was present vaginal misoprostol was repeated. Misoprostol only group (n = 9): four 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.
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.
Allocation concealment	A – Adequate

Study	**Bagratee 2004**
Methods	Computer-generated random allocation of study number. Numbered envelopes containing misoprostol or placebo.
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.
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.
Allocation concealment	A – Adequate

Study	**Creinin 1997**
Methods	Sealed, numbered, sequential envelopes containing instructions based on computer-generated random number table.
Participants	20 women with non-viable pregnancies diagnosed by transvaginal ultrasound; < 9 weeks; closed cervix; no contra-indication to misoprostol; no heavy bleeding.
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.

Characteristics of included studies (*Continued*)

Notes	Pilot study.
Allocation concealment	A – Adequate

Study	**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.
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 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) versus surgical evacuation of the uterus (n = 24).
Outcomes	Need for surgical evacuation, symptoms including pain and bleeding, 'satisfaction'.
Notes	Authors contacted for information on outcomes according to indication for treatment. Only usable data currently available are on incidence of surgical evacuation.
Allocation concealment	A – Adequate

Study	**Egarter 1995**
Methods	Women "randomly assigned"; no details.
Participants	87 women in Austria with non-viable pregnancies between 8 and 12 weeks, diagnosed by ultrasound.
Interventions	Vaginal gemeprost 1 mg every 3 hours up to maximum of 3 mg daily for 2 days (n = 43) versus uterine curettage (n = 44).
Outcomes	Need for surgical curettage. Adverse effects.
Notes	
Allocation concealment	B – Unclear

Study	**Eng 1997***
Methods	Randomised by "blindly picking a sealed number from a box". Treatment allocation was then based on whether the number was odd or even.
Participants	50 women with intrauterine fetal death at 13-26 weeks of pregnancy.
Interventions	Vaginal misoprostol 200 mcg 3-hourly up to a maximum dose of 1200 mcg (n = 25) versus vaginal gemeprost 1 mg 3-hourly up to a maximum dose of 5 mg (n = 25).
Outcomes	Main outcome - "treatment failure" defined as failure to miscarry within 24 hours, or side-effects severe enough to preclude use of additional dose of drug.
Notes	
Allocation concealment	C – Inadequate

Study	**Fadalla 2004***
Methods	"Randomised"; no details.
Participants	70 women in the Wad Medeni Teaching Hospital, Sudan, with fetal deaths between 13 and 28 weeks, diagnosed by ultrasound.
Interventions	Oral misoprostol (n = 35) versus vaginal misoprostol (n = 35) - both administered as 100 mcg tablets 4-hourly until initiation of labour.
Outcomes	Time to delivery; oxytocin infusion; manual removal of placenta.

Characteristics of included studies (*Continued*)

Notes	
Allocation concealment	B – Unclear

Study	**Gilles 2004**
Methods	Random allocation by computer-automated telephone response system. Stratification by pregnancy type. Random permuted blocks of size 4 or 8.
Participants	80 women with anembryonic pregnancy < 46 mm sac diameter or embryonic/fetal death with crown-rump length < 41 mm. Four centres.
Interventions	"Wet misoprostol" 800 mcg + 2 ml saline vaginally (n = 41) versus "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.
Notes	
Allocation concealment	A – Adequate

Study	**Graziosi 2004**
Methods	Consent for study obtained at time of diagnosis of early pregnancy failure. Randomised after at least one week of expectant management. Computer programme with block randomisation sequence. Stratification by previous vaginal birth; Gestational age < or > 10 weeks; centre.
Participants	154 women with ultrasound-diagnosed early pregnancy failure - either anembryonic pregnancy or fetal death at 6-14 weeks. 6 centre study in Netherlands.
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.
Notes	Of 241 eligible women, 87 (36%) declined to participate and chose curettage.
Allocation concealment	A – Adequate

Study	**Heard 2002**
Methods	"Randomized" - no details.
Participants	33 women with "missed abortion".
Interventions	Vaginal misoprostol 400 mcg (n = 12) versus 800 mcg (n = 21).
Outcomes	Only usable outcome reported in abstract was miscarriage.
Notes	Abstract - no explanation for unbalanced numbers.
Allocation concealment	B – Unclear

Study	**Herabutya 1997**
Methods	"Random allocation" but method not discussed in paper.
Participants	84 women with ultrasound confirmation of fetal death with uterine size < 14 weeks, no bleeding, and cervix closed.
Interventions	Misoprostol (200 micrograms vaginally) (n = 42) or vaginal placebo (n = 42) on admission to hospital.
Outcomes	Primary outcome was miscarriage within 24 hours of treatment. Some information available on complications.
Notes	Much of the outcome data reported describes only the subgroups who did miscarry before surgical evacuation.

Characteristics of included studies (*Continued*)

Allocation concealment	B – Unclear

Study	**Jain 1996***
Methods	"Random number table".
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) versus vaginal misoprostol 200 mcg 12-hourly alone.
Outcomes	Miscarriage.
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.
Allocation concealment	B – Unclear

Study	**Kara 1999***
Methods	"Random allocation". No details.
Participants	65 women in Istanbul, Turkey, with ultrasound-diagnosed fetal death in second trimester.
Interventions	Vaginal misoprostol 200 mcg (n = 32) versus intracervical dinoproston 0.5 mg (n = 33). Intravenous oxytocin started after 6 hours if no 'effective contractions'.
Outcomes	Complete miscarriage. Adverse effects.
Notes	Misoprostol dose reported as 200 mg. Assumed to be 200 mcg. Time to miscarriage not included as standard deviations seem incorrect.
Allocation concealment	B – Unclear

Study	**Kovavisarach 2002**
Methods	"Random allocation". Method not discussed.
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.
Notes	
Allocation concealment	B – Unclear

Study	**Kovavisarach 2005**
Methods	Random allocation using sealed, sequentially numbered envelopes, prepared using published table of random numbers.
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.
Notes	
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Lelaidier 1993**
Methods	Drug or identical placebo supplied by pharmacy using randomisation list using permutation blocks of four.
Participants	46 women with non-viable pregnancies diagnosed by ultrasound on two examinations separated by one 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.
Notes	Two 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.
Allocation concealment	A – Adequate

Study	**Lister 2005**
Methods	Random allocation - blocked and stratified by physician office and by day of recruitment - day of diagnosis, or after day of diagnosis.
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.
Notes	Planned sample size 84 but trial stopped after interim analysis of first 36 women. Two women excluded from analysis - one protocol violation; one did not meet entry criteria. Two women did not come for assessment 2 weeks after initial treatment.
Allocation concealment	A – Adequate

Study	**Muffley 2002**
Methods	Computer-generated random number table with blocked permutations - group assignments recorded in sealed opaque numbered envelopes.
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.
Notes	Analysis by intention to treat. Details about nausea, vomiting, diarrhoea reported only for misoprostol group.
Allocation concealment	A – Adequate

Study	**Ngoc 2004**
Methods	Randomised by opening sequentially numbered envelope - prepared by computer-generated code in blocks of 10.
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.

Characteristics of included studies (*Continued*)

Interventions	Oral misoprostol 800 mcg (n = 100) versus 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.
Notes	2 women lost to follow up.
Allocation concealment	A – Adequate

Study	**Nielsen 1999**
Methods	Randomisation method not discussed in paper.
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 micrograms) 48 hours later (n = 60) versus 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.
Notes	Seeking clarification from authors if "complex mass with deformed gestational sac" represents missed or incomplete miscarriage. Data included in meantime.
Allocation concealment	B – Unclear

Study	**Niromanesh 2005***
Methods	Randomisation method not discussed in paper.
Participants	100 women in Tehran, Iran, with fetal deaths between 14 and 25 weeks.
Interventions	Vaginal misoprostol: 400 mcg (n = 50) versus 600 mcg (n = 50) - both 12-hourly for 48 hours.
Outcomes	Miscarriage; surgical evacuation; adverse effects.
Notes	
Allocation concealment	B – Unclear

Study	**Tang 2003**
Methods	Randomisation by "computer-generated random numbers".
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 products of conception plus heavy bleeding.
Outcomes	Primary outcome: complete miscarriage (defined as no need for surgical evacuation up until return of menstruation).
Notes	
Allocation concealment	A – Adequate

Study	**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.

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.
Notes	Analysis by intention to treat.
Allocation concealment	A – Adequate

ERPC: evacuation of retained products of conception
hCG: human chorionic gonadotropin
IM: intramuscular
IU: international units
mcg: microgrammes
MTX: methotrexate
POCs: products of conception
TVS: transvaginal sonography
vs: versus

Characteristics of excluded studies

Study	Reason for exclusion
Abdel Fattah 1997	Conference abstract. No information about gestational age but, given title, probably includes pregnancies > 24 weeks as well as < 24 weeks.
Almog 2005	Termination of 'viable' pregnancies - mainly with fetal anomalies.
Anderman 2000	Conference abstract. Includes pregnancies > 24 weeks as well as < 24 weeks.
Avila-Vergara 1997	Intrauterine deaths mainly third trimester.
Bebbington 2002	Termination of viable pregnancies.
Cabrol 1990	Trial of mifepristone for induction of labour after intrauterine death - but mainly late second and third trimester pregnancies.
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 twelve weeks of gestation. Three 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.
David 2003	Randomised trial (details of randomisation unclear) of two methods to soften the cervix before surgical evacuation for early non-viable pregnancies. No usable clinical data, given short timescale between treatment and surgery.
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. Data will be included for the latter if these can be obtained from the authors.
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. Data will be included for the latter if these can be obtained from the authors.
Dickinson 2003	Randomised trial comparing oral with vaginal administration of misoprostol to terminate pregnancies with fetal malformations - not non-viable pregnancies.

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. Data will be included for the latter if these can be obtained from the authors.
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. Data will be included for the latter if these can be obtained from the authors.
Ghorab 1998	Trial included women with fetal malformations for pregnancy termination, as well as pregnancies with fetal death. Data will be included for the latter if these can be obtained from the authors.
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. Data will be included for the latter if these can be obtained from the authors.
Grimes 2004	Trial included women with other reasons for pregnancy termination, as well as pregnancies with fetal death. Data will be included for the latter if these can be obtained from the authors.
Gronland 2002	Not a randomised trial. Three centre study of women with non-viable pregnancies comparing three treatment regimens: misoprostol, mifepristone + misoprostol, surgical evacuation - with treatment regimen changing at each hospital every four months.
Hausler 1997	Prospective randomised controlled trial evaluating three 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, one did not report for curettage, in one the height of the endometrium was > 8 mm and in one 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.
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. Data will be included for the latter if these can be obtained from the authors.
Hill 1991	Trial includes fetal deaths in both second and third trimesters.
Hogg 2000	Abstract. Trial included women with other reasons for pregnancy termination, as well as pregnancies with fetal death. Data will be included for the latter if these can be obtained from the authors.
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. Data will be included for the latter if these can be obtained from the authors.
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. Data will be included for the latter if these can be obtained from the authors.
Johnson 1997	Randomised controlled trial evaluating pain and bleeding and comparing surgical to medical treatment. Surgical arm (n = 12) uterine curettage under general anesthesia. Medical arm (n = 17) include three different participant conditions and treatments: a) no treatment if women had a complete abortion and uterine cavity echo (nyometrium-myometrium) less than 1.5 mm; b) women with incomplete abortion : 1 mg pessary of Gemeprost (Cervagem, May and Baker) and remained in hospital for 4 hours or until the 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.
Kanhai 1989	Includes both second and third trimester fetal deaths.
Lippert 1978	Second and third trimester fetal deaths. Not obviously randomised.

Characteristics of excluded studies (*Continued*)

Machtinger 2002	Abstract. Appears to include both non-viable pregnancies and miscarriages. Await full report.
Machtinger 2004	Abstract. Appears to include both non-viable pregnancies and miscarriages. Await full report.
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.
Nakintu 2001	Both second and third trimester fetal deaths. Seeking separate data from author.
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.
Nuthalapaty 2004	Abstract. Clinical indications for termination not described.
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. Data will be included for the latter if these can be obtained from the authors.
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. Data will be included for the latter if these can be obtained from the authors.
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.
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.
Ramsey 2004	Trial included women with other reasons for pregnancy termination, as well as pregnancies with fetal death. Data will be included for the latter if these can be obtained from the authors.
Roy 2003	Abstract. Not clear if fetal death included as indication for termination.
Salamalekis 1990	Abstract only. Treatment allocation by alternation, not by randomisation.
Su 2005	Termination of pregnancy for fetal anomalies, social reasons or maternal disease; not for non-viable pregnancies.
Surita 1997	Abstract only. May include third trimester fetal deaths.
Thavarasah 1986	Unclear from paper but allocation may have been by alternation. Will seek clarification from authors.
Toppozada 1994	Includes third trimester fetal deaths.
Yapar 1996	Includes indications for termination other than fetal death. High degree of protocol violation (60/400). Results not presented as intention-to-treat.
Zhang 2005	Includes both non-viable pregnancies and miscarriages. Data will be included for the former if these can be obtained from the authors.

hCG: human chorionic gonadotropin
POC: products of conception
RCT: randomised controlled trial

Characteristics of ongoing studies

Study	**Australia 2000**
Trial name or title	Misoprostol for the medical management of miscarriage (randomised controlled trial).
Participants	Women with a spontaneous incomplete or missed abortion up to and including 12 weeks' gestation.
Interventions	Drugs and medications; surgery.
Outcomes	Primary outcome measures: (1) need for evacuation of retained products of conception in theatre within 1 month of the intervention; (2) infection requiring antibiotics;

Characteristics of ongoing studies (*Continued*)

	(3) change in haemoglobin from pre-intervention to 72 hours and 4 weeks post-intervention. Secondary outcomes: (1) side-effects e.g. nausea, vomiting, diarrhoea, abdominal pain; (2) analgesia required in hospital - narcotics or oral; (3) antiemetics required in hospital; (4) duration of bleeding; (5) complication rates based on ethnic extraction.
Starting date	April 1999.
Contact information	Katharine Louey 7 Eagle 11 Bridge Rd Mackay Qld 4740 Australia Tel: + 61 7 49531817 e-mail: klouey@mrbean.net.au
Notes	

Study	**UK 1999**
Trial name or title	Miscarriage Treatment Study (MIST).
Participants	Women with confirmed missed and incomplete miscarriage attending early pregnancy clinics, with gestational dates less than 91 days (13 weeks), or uterine cavity volume being less than 91 days. Other inclusion criteria: women can understand English, willing to be randomised to any treatment group and there is uncertainty about the best management. Exclusion criteria: severe haemorrhage, severe pain, pyrexia above 37.5 C, severe asthma, blood dyscrasia, diabetes, current anticoagulants or corticosteroid therapy, twin or higher order pregnancy, use of prostaglandin contra-indicated, cannot understand written English, refuses written consent.
Interventions	Expectant group: sent home with written advice and analgesia. Medical group: will be admitted (immediately if incomplete miscarriage and 24-48 hours after oral administration of mifepristone if missed miscarriage) and vaginal misoprostol will be administered. Surgical group: as is current practice.
Outcomes	Primary outcome measure: (1) gynecological infection within 14 days of the confirmation of miscarriage by TVS. Secondary outcome measures: (1) treatment with antibiotic (within 14 days and 6 weeks); (2) days of pain, days of vaginal bleeding, time off work, return to usual daily activities; (3) haemoglobin and packed cell volume (both at 10-14 days), unplanned surgical ERPC or other admission (within 14 days or 6 weeks); (4) complete evacuation of the uterus by TVS (at 10-14 days); (5) depression anxiety and general health (at 6 weeks).
Starting date	
Contact information	Miss Lohanna Trinder MIST Study Co-ordinating Center Dept of Women's Health Cotswold Center Southmead Hospital Bristol BS10 5NB UK Tel: 01179595186 FAX 01179595178 e-mail: jo_trinder@msn.com.uk
Notes	

ERPC: evacuation of retained products of conception

Characteristics of ongoing studies (*Continued*)

TVS: transvaginal sonography

ANALYSES

Comparison 01. Vaginal misoprostol versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Complete miscarriage < 24 hours after treatment	2	138	Relative Risk (Fixed) 95% CI	4.73 [2.70, 8.28]
02 Complete miscarriage < 48 hours	2	84	Relative Risk (Fixed) 95% CI	5.74 [2.70, 12.19]
03 Complete miscarriage without ERPC day 7	1	83	Relative Risk (Fixed) 95% CI	2.99 [1.80, 4.99]
04 Uterine curettage	2	104	Relative Risk (Fixed) 95% CI	0.40 [0.26, 0.60]
05 Opiates for pain relief	1	84	Relative Risk (Fixed) 95% CI	5.00 [0.25, 101.11]
06 Blood transfusion	1	84	Relative Risk (Fixed) 95% CI	0.20 [0.01, 4.04]
07 Haemoglobin difference > 10 g/L	1	50	Relative Risk (Fixed) 95% CI	1.25 [0.38, 4.12]
08 Nausea	2	88	Relative Risk (Fixed) 95% CI	1.38 [0.43, 4.40]
09 Diarrhoea	2	88	Relative Risk (Fixed) 95% CI	2.21 [0.35, 14.06]
10 Fever	1	54	Relative Risk (Fixed) 95% CI	9.00 [0.51, 159.43]
11 Uterine perforation	1	84	Relative Risk (Fixed) 95% CI	0.33 [0.01, 7.96]
12 Vaginal bleeding 2 weeks after treatment	1	32	Relative Risk (Fixed) 95% CI	1.00 [0.41, 2.45]
13 Satisfaction with treatment	1	32	Relative Risk (Fixed) 95% CI	1.17 [0.83, 1.64]

Comparison 02. Vaginal misoprostol versus surgical evacuation of uterus

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Surgical evacuation of uterus	3	254	Relative Risk (Fixed) 95% CI	0.42 [0.34, 0.52]
02 Post-treatment haematocrit (%)	1	50	Weighted Mean Difference (Fixed) 95% CI	-1.40 [-3.51, 0.71]
03 Nausea	1	154	Relative Risk (Fixed) 95% CI	21.85 [1.31, 364.37]
04 Pain relief	1	154	Relative Risk (Fixed) 95% CI	1.42 [0.82, 2.46]
05 Diarrhoea	1	154	Relative Risk (Fixed) 95% CI	40.85 [2.52, 662.57]
06 Uterine perforation	1	154	Relative Risk (Fixed) 95% CI	0.32 [0.01, 7.65]
07 Asherman syndrome	1	154	Relative Risk (Fixed) 95% CI	0.32 [0.01, 7.65]

Comparison 03. Vaginal misoprostol versus vaginal gemeprost

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Miscarriage < 24 hours	1	50	Relative Risk (Fixed) 95% CI	1.24 [0.90, 1.70]
02 Temperature > 38 degrees C	1	50	Relative Risk (Fixed) 95% CI	1.50 [0.27, 8.22]
03 Vomiting	1	50	Relative Risk (Fixed) 95% CI	3.00 [0.13, 70.30]
04 Diarrhoea	1	50	Relative Risk (Fixed) 95% CI	0.14 [0.01, 2.63]
05 Opiate analgesia	1	50	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 04. Vaginal misoprostol versus vaginal prostaglandin E1/2

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Surgical evacuation	1	60	Relative Risk (Fixed) 95% CI	0.39 [0.21, 0.72]
02 Blood transfusion	1	60	Relative Risk (Fixed) 95% CI	6.07 [0.30, 121.33]
03 Hospital stay (days)	1	60	Weighted Mean Difference (Fixed) 95% CI	-2.38 [-3.36, -1.40]
04 Complete miscarriage	1	65	Relative Risk (Fixed) 95% CI	1.44 [1.06, 1.96]
05 Nausea	1	65	Relative Risk (Fixed) 95% CI	1.03 [0.28, 3.78]

Comparison 05. Vaginal misoprostol lower versus higher dose regimens

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Miscarriage	3	247	Relative Risk (Fixed) 95% CI	0.85 [0.72, 1.00]
02 Fever	2	214	Relative Risk (Fixed) 95% CI	0.73 [0.41, 1.30]
03 Nausea	2	214	Relative Risk (Fixed) 95% CI	0.67 [0.31, 1.41]
04 Diarrhoea	2	214	Relative Risk (Fixed) 95% CI	0.54 [0.15, 1.91]

Comparison 06. Vaginal misoprostol wet versus dry vaginal preparations

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Miscarriage < 3 days	1	80	Relative Risk (Fixed) 95% CI	1.14 [0.85, 1.54]
02 Miscarriage < 8 days	1	80	Relative Risk (Fixed) 95% CI	1.04 [0.84, 1.29]
03 Miscarriage < 15 days	1	80	Relative Risk (Fixed) 95% CI	0.92 [0.78, 1.10]
04 Miscarriage < 30 days	1	80	Relative Risk (Fixed) 95% CI	0.95 [0.79, 1.14]
05 Diarrhoea < 48 hours after treatment	1	77	Relative Risk (Fixed) 95% CI	1.75 [0.89, 3.42]
06 Chills < 48 hours of treatment	1	77	Relative Risk (Fixed) 95% CI	1.36 [0.94, 1.98]
07 Vomiting < 48 hours of treatment	1	77	Relative Risk (Fixed) 95% CI	0.93 [0.33, 2.62]
08 Would wish/probably wish same treatment in future nonviable pregnancy	1	73	Relative Risk (Fixed) 95% CI	1.18 [0.93, 1.49]

Comparison 07. Vaginal misoprostol + methotrexate versus vaginal misoprostol alone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Miscarriage not complete	1	21	Relative Risk (Fixed) 95% CI	0.26 [0.01, 5.65]
04 Additional surgical evacuation	1	21	Relative Risk (Fixed) 95% CI	0.26 [0.01, 5.65]
05 Haemorrhage	1	21	Relative Risk (Fixed) 95% CI	2.31 [0.10, 50.85]
06 Pain relief	1	21	Relative Risk (Fixed) 95% CI	0.75 [0.25, 2.22]

Comparison 08. Vaginal misoprostol plus laminaria tents versus vaginal misoprostol alone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Miscarriage < 24 hours	1	38	Relative Risk (Fixed) 95% CI	0.90 [0.65, 1.25]
02 Miscarriage < 48 hours	1	38	Relative Risk (Fixed) 95% CI	1.07 [0.88, 1.29]

Comparison 09. Oral misoprostol versus vaginal misoprostol

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Complete miscarriage	2	218	Relative Risk (Fixed) 95% CI	0.90 [0.82, 0.99]
02 Vomiting	1	190	Relative Risk (Fixed) 95% CI	0.29 [0.10, 0.84]
09 Nausea	1	20	Relative Risk (Fixed) 95% CI	0.80 [0.37, 1.74]
10 Diarrhoea	2	210	Relative Risk (Fixed) 95% CI	1.05 [0.67, 1.66]
12 Pain (visual analogue scale)	1	18	Weighted Mean Difference (Fixed) 95% CI	-1.90 [-4.82, 1.02]
13 Fever	1	190	Relative Risk (Fixed) 95% CI	1.00 [0.36, 2.74]
14 Women's satisfaction with treatment	1	198	Relative Risk (Fixed) 95% CI	0.96 [0.86, 1.06]
15 Time to delivery (hours)	1	70	Weighted Mean Difference (Fixed) 95% CI	4.10 [2.64, 5.56]
16 Oxytocin infusion	1	70	Relative Risk (Fixed) 95% CI	2.75 [0.97, 7.81]
17 Manual removal of placenta	1	70	Relative Risk (Fixed) 95% CI	4.50 [1.05, 19.35]

Comparison 10. Oral misoprostol + mifepristone versus expectant management

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Empty uterine cavity at day 5	1	122	Relative Risk (Fixed) 95% CI	1.08 [0.90, 1.30]
02 Urgent surgical evacuation for bleeding	1	122	Relative Risk (Fixed) 95% CI	0.34 [0.01, 8.29]
03 Pelvic inflammatory disease	1	122	Relative Risk (Fixed) 95% CI	0.52 [0.05, 5.55]
04 Pain (visual analogue scale day 5)	1	122	Weighted Mean Difference (Fixed) 95% CI	4.10 [-5.92, 14.12]
05 Sick leave (days)	1	122	Weighted Mean Difference (Fixed) 95% CI	1.80 [0.63, 2.97]
06 Bleeding (days)	1	122	Weighted Mean Difference (Fixed) 95% CI	0.70 [-0.43, 1.83]
07 Satisfaction with treatment (visual analogue scale day 14)	1	122	Weighted Mean Difference (Fixed) 95% CI	3.40 [-5.54, 12.34]

Comparison 11. Sublingual misoprostol versus vaginal misoprostol

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Complete miscarriage	1	80	Relative Risk (Fixed) 95% CI	1.00 [0.85, 1.18]
02 Nausea	1	80	Relative Risk (Fixed) 95% CI	1.20 [0.80, 1.79]
03 Vomiting	1	80	Relative Risk (Fixed) 95% CI	0.78 [0.32, 1.88]
04 Diarrhoea	1	80	Relative Risk (Fixed) 95% CI	2.55 [1.48, 4.38]
05 Haemoglobin day 43	1	80	Weighted Mean Difference (Fixed) 95% CI	0.10 [-0.38, 0.58]
06 Intolerable pain	1	80	Relative Risk (Fixed) 95% CI	0.75 [0.29, 1.97]
07 Satisfied with treatment	1	77	Relative Risk (Fixed) 95% CI	0.99 [0.79, 1.25]

Comparison 12. Mifepristone versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Miscarriage < 48 hours	1	46	Relative Risk (Fixed) 95% CI	5.00 [0.25, 98.75]
02 Miscarriage < 3 days	1	46	Relative Risk (Fixed) 95% CI	19.00 [1.17, 308.40]
03 Miscarriage < 4 days	1	46	Relative Risk (Fixed) 95% CI	14.00 [2.00, 97.88]
04 Miscarriage < 5 days	1	46	Relative Risk (Fixed) 95% CI	9.50 [2.49, 36.19]
05 Vaginal bleeding before day 5	1	44	Relative Risk (Fixed) 95% CI	4.20 [1.95, 9.03]
06 Pain before day 5	1	44	Relative Risk (Fixed) 95% CI	2.19 [0.93, 5.17]

Comparison 13. Vaginal gemeprost versus surgical evacuation of uterus

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Surgical evacuation	1	87	Relative Risk (Fixed) 95% CI	0.23 [0.14, 0.40]
02 Perforation of uterus	1	87	Relative Risk (Fixed) 95% CI	0.20 [0.01, 4.14]
03 Nausea	1	87	Relative Risk (Fixed) 95% CI	1.79 [0.56, 5.68]

INDEX TERMS

Medical Subject Headings (MeSH)

Abortifacient Agents [*therapeutic use]; Abortion, Induced [*methods]; Administration, Intravaginal; Administration, Oral; *Fetal Death [ultrasonography]; Mifepristone [*therapeutic use]; Misoprostol [*therapeutic use]; Randomized Controlled Trials; Ultrasonography, Prenatal

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Medical treatment for early fetal death (less than 24 weeks)
Authors	Neilson JP, Hickey M, Vazquez J
Contribution of author(s)	Juan Vazquez: protocol development and revisions to first draft of review. Martha Hickey: protocol development and revisions to the first draft of review. Jim Neilson: supervision of protocol development; completion of first draft of review.
Issue protocol first published	2000/3
Review first published	2006/3
Date of most recent amendment	17 May 2006
Date of most recent SUBSTANTIVE amendment	24 April 2006
What's New	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 will now address these topics - thus, the change in title.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author

Date new studies found and included/excluded	30 November 2005
Date authors' conclusions section amended	Information not supplied by author
Contact address	Prof James P Neilson Professor of Obstetrics and Gynaecology/Head of School of Reproductive and Developmental Medicine Division of Perinatal and Reproductive Medicine The University of Liverpool First Floor Liverpool Women's NHS Foundation Trust, Crown Street Liverpool L8 7SS UK E-mail: jneilson@liverpool.ac.uk Tel: +44 151 7024100 Fax: +44 151 7024024
DOI	10.1002/14651858.CD002253.pub3
Cochrane Library number	CD002253
Editorial group	Cochrane Pregnancy and Childbirth Group
Editorial group code	HM-PREG

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Vaginal misoprostol versus placebo, Outcome 01 Complete miscarriage < 24 hours after treatment

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 01 Complete miscarriage < 24 hours after treatment

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Herabutya 1997	35/42	6/42		54.5	5.83 [2.75, 12.39]
Kovavisarach 2002	17/27	5/27		45.5	3.40 [1.46, 7.89]
Total (95% CI)	69	69		100.0	4.73 [2.70, 8.28]
Total events: 52 (Misoprostol), 11 (Placebo)					
Test for heterogeneity chi-square=0.89 df=1 p=0.35 I^2 =0.0%					
Test for overall effect z=5.44 p<0.00001					

Analysis 01.02. Comparison 01 Vaginal misoprostol versus placebo, Outcome 02 Complete miscarriage < 48 hours

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 02 Complete miscarriage < 48 hours

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lister 2005	15/18	2/16		34.6	6.67 [1.79, 24.78]
Wood 2002	21/25	4/25		65.4	5.25 [2.10, 13.10]
Total (95% CI)	43	41		100.0	5.74 [2.70, 12.19]
Total events: 36 (Misoprostol), 6 (Placebo)					
Test for heterogeneity chi-square=0.09 df=1 p=0.77 I^2 =0.0%					
Test for overall effect z=4.55 p<0.00001					

Analysis 01.03. Comparison 01 Vaginal misoprostol versus placebo, Outcome 03 Complete miscarriage without ERPC day 7

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 03 Complete miscarriage without ERPC day 7

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bagratee 2004	39/45	11/38		100.0	2.99 [1.80, 4.99]
Total (95% CI)	45	38		100.0	2.99 [1.80, 4.99]
Total events: 39 (Treatment), 11 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.20 p=0.00003					

Analysis 01.04. Comparison 01 Vaginal misoprostol versus placebo, Outcome 04 Uterine curettage

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 04 Uterine curettage

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kovavisarach 2002	10/27	22/27		51.2	0.45 [0.27, 0.77]
Wood 2002	7/25	21/25		48.8	0.33 [0.17, 0.64]
Total (95% CI)	52	52		100.0	0.40 [0.26, 0.60]

Total events: 17 (Misoprostol), 43 (Placebo)

Test for heterogeneity chi-square=0.54 df=1 p=0.46 I^2 =0.0%

Test for overall effect z=4.44 p<0.00001

Analysis 01.05. Comparison 01 Vaginal misoprostol versus placebo, Outcome 05 Opiates for pain relief

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 05 Opiates for pain relief

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Herabutya 1997	2/42	0/42		100.0	5.00 [0.25, 101.11]
Total (95% CI)	42	42		100.0	5.00 [0.25, 101.11]

Total events: 2 (Misoprostol), 0 (Placebo)

Test for heterogeneity: not applicable

Test for overall effect z=1.05 p=0.3

Analysis 01.06. Comparison 01 Vaginal misoprostol versus placebo, Outcome 06 Blood transfusion

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 06 Blood transfusion

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Herabutya 1997	0/42	2/42		100.0	0.20 [0.01, 4.04]
Total (95% CI)	42	42		100.0	0.20 [0.01, 4.04]
Total events: 0 (Misoprostol), 2 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.05 p=0.3					

Analysis 01.07. Comparison 01 Vaginal misoprostol versus placebo, Outcome 07 Haemoglobin difference > 10 g/L

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 07 Haemoglobin difference > 10 g/L

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Wood 2002	5/25	4/25		100.0	1.25 [0.38, 4.12]
Total (95% CI)	25	25		100.0	1.25 [0.38, 4.12]
Total events: 5 (Misoprostol), 4 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.37 p=0.7					

Analysis 01.08. Comparison 01 Vaginal misoprostol versus placebo, Outcome 08 Nausea

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 08 Nausea

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kovavisarach 2002	2/27	1/27		23.9	2.00 [0.19, 20.77]
Lister 2005	4/18	3/16		76.1	1.19 [0.31, 4.51]
Total (95% CI)	45	43		100.0	1.38 [0.43, 4.40]

Total events: 6 (Misoprostol), 4 (Placebo)

Test for heterogeneity chi-square=0.15 df=1 p=0.70 I^2 =0.0%

Test for overall effect z=0.55 p=0.6

Analysis 01.09. Comparison 01 Vaginal misoprostol versus placebo, Outcome 09 Diarrhoea

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 09 Diarrhoea

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kovavisarach 2002	2/27	0/27		32.1	5.00 [0.25, 99.51]
Lister 2005	1/18	1/16		67.9	0.89 [0.06, 13.08]
Total (95% CI)	45	43		100.0	2.21 [0.35, 14.06]

Total events: 3 (Misoprostol), 1 (Placebo)

Test for heterogeneity chi-square=0.73 df=1 p=0.39 I^2 =0.0%

Test for overall effect z=0.84 p=0.4

Analysis 01.10. Comparison 01 Vaginal misoprostol versus placebo, Outcome 10 Fever

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 10 Fever

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kovavisarach 2002	4/27	0/27		100.0	9.00 [0.51, 159.43]
Total (95% CI)	27	27		100.0	9.00 [0.51, 159.43]
Total events: 4 (Misoprostol), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.50 p=0.1					

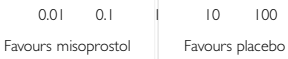
Analysis 01.11. Comparison 01 Vaginal misoprostol versus placebo, Outcome 11 Uterine perforation

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 11 Uterine perforation

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Herabutya 1997	0/42	1/42		100.0	0.33 [0.01, 7.96]
Total (95% CI)	42	42		100.0	0.33 [0.01, 7.96]
Total events: 0 (Misoprostol), 1 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					



Analysis 01.12. Comparison 01 Vaginal misoprostol versus placebo, Outcome 12 Vaginal bleeding 2 weeks after treatment

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 12 Vaginal bleeding 2 weeks after treatment

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lister 2005	6/16	6/16		100.0	1.00 [0.41, 2.45]
Total (95% CI)	16	16		100.0	1.00 [0.41, 2.45]

Total events: 6 (Misoprostol), 6 (Placebo)

Test for heterogeneity: not applicable

Test for overall effect z=0.00 p=1

Analysis 01.13. Comparison 01 Vaginal misoprostol versus placebo, Outcome 13 Satisfaction with treatment

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

Comparison: 01 Vaginal misoprostol versus placebo

Outcome: 13 Satisfaction with treatment

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lister 2005	14/16	12/16		100.0	1.17 [0.83, 1.64]
Total (95% CI)	16	16		100.0	1.17 [0.83, 1.64]

Total events: 14 (Misoprostol), 12 (Placebo)

Test for heterogeneity: not applicable

Test for overall effect z=0.89 p=0.4

Analysis 02.01. Comparison 02 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 01 Surgical evacuation of uterus

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

Comparison: 02 Vaginal misoprostol versus surgical evacuation of uterus

Outcome: 01 Surgical evacuation of uterus

Study	Vaginal misoprostol n/N	Surgical evacuation n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Demetroulis 2001	6/26	24/24		20.3	0.23 [0.11, 0.47]
Graziosi 2004	37/79	73/75		61.0	0.48 [0.38, 0.61]
Muffley 2002	10/25	23/25		18.7	0.43 [0.27, 0.71]
Total (95% CI)	130	124		100.0	0.42 [0.34, 0.52]

Total events: 53 (Vaginal misoprostol), 120 (Surgical evacuation)

Test for heterogeneity chi-square=4.03 df=2 p=0.13 I^2 =50.4%

Test for overall effect z=8.07 p<0.00001

Analysis 02.02. Comparison 02 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 02 Post-treatment haematocrit (%)

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

Comparison: 02 Vaginal misoprostol versus surgical evacuation of uterus

Outcome: 02 Post-treatment haematocrit (%)

Study	Misoprostol N	Misoprostol Mean(SD)	Surgical evacuation N	Surgical evacuation Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Muffley 2002	25	34.10 (5.00)	25	35.50 (2.00)		100.0	-1.40 [-3.51, 0.71]
Total (95% CI)	25		25			100.0	-1.40 [-3.51, 0.71]

Test for heterogeneity: not applicable

Test for overall effect z=1.30 p=0.2

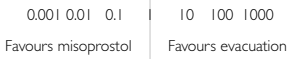
Analysis 02.03. Comparison 02 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 03 Nausea

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

Comparison: 02 Vaginal misoprostol versus surgical evacuation of uterus

Outcome: 03 Nausea

Study	Misoprostol n/N	Evacuation n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Graziosi 2004	11/79	0/75		100.0	21.85 [1.31, 364.37]
Total (95% CI)	79	75		100.0	21.85 [1.31, 364.37]
Total events: 11 (Misoprostol), 0 (Evacuation)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.15 p=0.03					



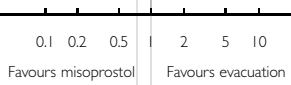
Analysis 02.04. Comparison 02 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 04 Pain relief

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

Comparison: 02 Vaginal misoprostol versus surgical evacuation of uterus

Outcome: 04 Pain relief

Study	Misoprostol n/N	Evacuation n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Graziosi 2004	24/79	16/75		100.0	1.42 [0.82, 2.46]
Total (95% CI)	79	75		100.0	1.42 [0.82, 2.46]
Total events: 24 (Misoprostol), 16 (Evacuation)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.26 p=0.2					



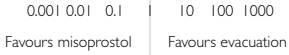
Analysis 02.05. Comparison 02 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 05 Diarrhoea

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

Comparison: 02 Vaginal misoprostol versus surgical evacuation of uterus

Outcome: 05 Diarrhoea

Study	Misoprostol n/N	Evacuation n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Graziosi 2004	21/79	0/75		100.0	40.85 [2.52, 662.57]
Total (95% CI)	79	75		100.0	40.85 [2.52, 662.57]
Total events: 21 (Misoprostol), 0 (Evacuation)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.61 p=0.009					



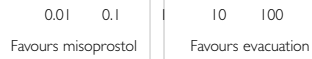
Analysis 02.06. Comparison 02 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 06 Uterine perforation

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

Comparison: 02 Vaginal misoprostol versus surgical evacuation of uterus

Outcome: 06 Uterine perforation

Study	Misoprostol n/N	Evacuation n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Graziosi 2004	0/79	1/75		100.0	0.32 [0.01, 7.65]
Total (95% CI)	79	75		100.0	0.32 [0.01, 7.65]
Total events: 0 (Misoprostol), 1 (Evacuation)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.71 p=0.5					

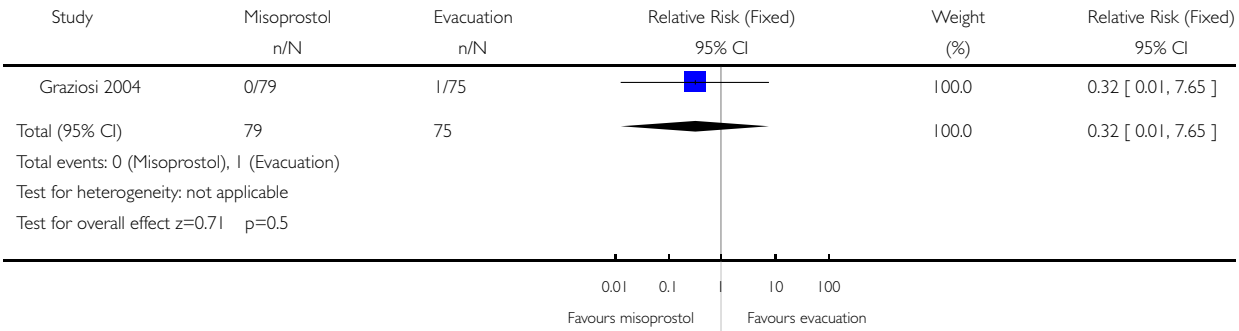


Analysis 02.07. Comparison 02 Vaginal misoprostol versus surgical evacuation of uterus, Outcome 07 Asherman syndrome

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

Comparison: 02 Vaginal misoprostol versus surgical evacuation of uterus

Outcome: 07 Asherman syndrome

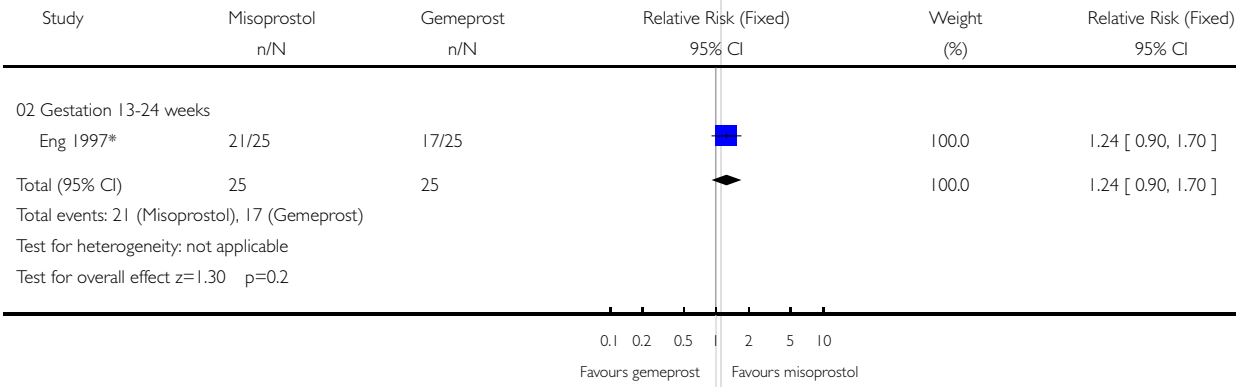


Analysis 03.01. Comparison 03 Vaginal misoprostol versus vaginal gemeprost, Outcome 01 Miscarriage < 24 hours

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

Comparison: 03 Vaginal misoprostol versus vaginal gemeprost

Outcome: 01 Miscarriage < 24 hours



Analysis 03.02. Comparison 03 Vaginal misoprostol versus vaginal gemeprost, Outcome 02 Temperature > 38 degrees C

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

Comparison: 03 Vaginal misoprostol versus vaginal gemeprost

Outcome: 02 Temperature > 38 degrees C

Study	Misoprostol n/N	Gemeprost n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
02 Gestation 13-24 weeks					
Eng 1997*	3/25	2/25		100.0	1.50 [0.27, 8.22]
Total (95% CI)	25	25		100.0	1.50 [0.27, 8.22]
Total events: 3 (Misoprostol), 2 (Gemeprost)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.47 p=0.6					

Analysis 03.03. Comparison 03 Vaginal misoprostol versus vaginal gemeprost, Outcome 03 Vomiting

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

Comparison: 03 Vaginal misoprostol versus vaginal gemeprost

Outcome: 03 Vomiting

Study	Misoprostol n/N	Gemeprost n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
02 Gestation 13-24 weeks					
Eng 1997*	1/25	0/25		100.0	3.00 [0.13, 70.30]
Total (95% CI)	25	25		100.0	3.00 [0.13, 70.30]
Total events: 1 (Misoprostol), 0 (Gemeprost)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					

Analysis 03.04. Comparison 03 Vaginal misoprostol versus vaginal gemeprost, Outcome 04 Diarrhoea

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

Comparison: 03 Vaginal misoprostol versus vaginal gemeprost

Outcome: 04 Diarrhoea

Study	Misoprostol n/N	Gemeprost n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
02 Gestation 13-24 weeks					
Eng 1997*	0/25	3/25		100.0	0.14 [0.01, 2.63]
Total (95% CI)	25	25		100.0	0.14 [0.01, 2.63]
Total events: 0 (Misoprostol), 3 (Gemeprost)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.31 p=0.2					

Analysis 03.05. Comparison 03 Vaginal misoprostol versus vaginal gemeprost, Outcome 05 Opiate analgesia

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

Comparison: 03 Vaginal misoprostol versus vaginal gemeprost

Outcome: 05 Opiate analgesia

Study	Misoprostol n/N	Gemeprost n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
02 Gestation 13-24 weeks					
× Eng 1997*	0/25	0/25		0.0	Not estimable
Total (95% CI)	25	25		0.0	Not estimable
Total events: 0 (Misoprostol), 0 (Gemeprost)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 04.01. Comparison 04 Vaginal misoprostol versus vaginal prostaglandin E1/2, Outcome 01 Surgical evacuation

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

Comparison: 04 Vaginal misoprostol versus vaginal prostaglandin E1/2

Outcome: 01 Surgical evacuation

Study	Misoprostol n/N	PGE2 n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Al Inizi 2003	8/27	25/33		100.0	0.39 [0.21, 0.72]
Total (95% CI)	27	33		100.0	0.39 [0.21, 0.72]
Total events: 8 (Misoprostol), 25 (PGE2)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.00 p=0.003					

Analysis 04.02. Comparison 04 Vaginal misoprostol versus vaginal prostaglandin E1/2, Outcome 02 Blood transfusion

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

Comparison: 04 Vaginal misoprostol versus vaginal prostaglandin E1/2

Outcome: 02 Blood transfusion

Study	Misoprostol n/N	PGE2 n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Al Inizi 2003	2/27	0/33		100.0	6.07 [0.30, 121.33]
Total (95% CI)	27	33		100.0	6.07 [0.30, 121.33]
Total events: 2 (Misoprostol), 0 (PGE2)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.18 p=0.2					

Analysis 04.03. Comparison 04 Vaginal misoprostol versus vaginal prostaglandin E1/2, Outcome 03 Hospital stay (days)

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

Comparison: 04 Vaginal misoprostol versus vaginal prostaglandin E1/2

Outcome: 03 Hospital stay (days)

Study	Misoprostol N	Misoprostol Mean(SD)	PGE2 N	PGE2 Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Al Inizi 2003	27	1.62 (0.56)	33	4.00 (2.80)		100.0	-2.38 [-3.36, -1.40]
Total (95% CI)	27		33			100.0	-2.38 [-3.36, -1.40]
Test for heterogeneity: not applicable							
Test for overall effect z=4.77 p<0.00001							

Analysis 04.04. Comparison 04 Vaginal misoprostol versus vaginal prostaglandin E1/2, Outcome 04 Complete miscarriage

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

Comparison: 04 Vaginal misoprostol versus vaginal prostaglandin E1/2

Outcome: 04 Complete miscarriage

Study	Misoprostol n/N	PGE2 n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kara 1999*	28/32	20/33		100.0	1.44 [1.06, 1.96]
Total (95% CI)	32	33		100.0	1.44 [1.06, 1.96]
Total events: 28 (Misoprostol), 20 (PGE2)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.36 p=0.02					

Analysis 04.05. Comparison 04 Vaginal misoprostol versus vaginal prostaglandin E1/2, Outcome 05 Nausea

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

Comparison: 04 Vaginal misoprostol versus vaginal prostaglandin E1/2

Outcome: 05 Nausea

Study	Misoprostol n/N	PGE2 n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kara 1999*	4/32	4/33		100.0	1.03 [0.28, 3.78]
Total (95% CI)	32	33		100.0	1.03 [0.28, 3.78]
Total events: 4 (Misoprostol), 4 (PGE2)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.05 p=1					

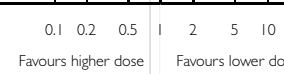
Analysis 05.01. Comparison 05 Vaginal misoprostol lower versus higher dose regimens, Outcome 01 Miscarriage

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

Comparison: 05 Vaginal misoprostol lower versus higher dose regimens

Outcome: 01 Miscarriage

Study	Lower n/N	Higher n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 400 mcg versus 600 mcg					
Niromanesh 2005*	42/50	40/50		44.1	1.05 [0.87, 1.26]
Subtotal (95% CI)	50	50		44.1	1.05 [0.87, 1.26]
Total events: 42 (Lower), 40 (Higher)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.52 p=0.6					
02 400 mcg versus 800 mcg					
Heard 2002	7/12	16/21		12.8	0.77 [0.45, 1.31]
Subtotal (95% CI)	12	21		12.8	0.77 [0.45, 1.31]
Total events: 7 (Lower), 16 (Higher)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.98 p=0.3					
03 600 mcg versus 800 mcg					
Kovavisarach 2005	26/57	39/57		43.0	0.67 [0.48, 0.93]
Subtotal (95% CI)	57	57		43.0	0.67 [0.48, 0.93]
Total events: 26 (Lower), 39 (Higher)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.38 p=0.02					



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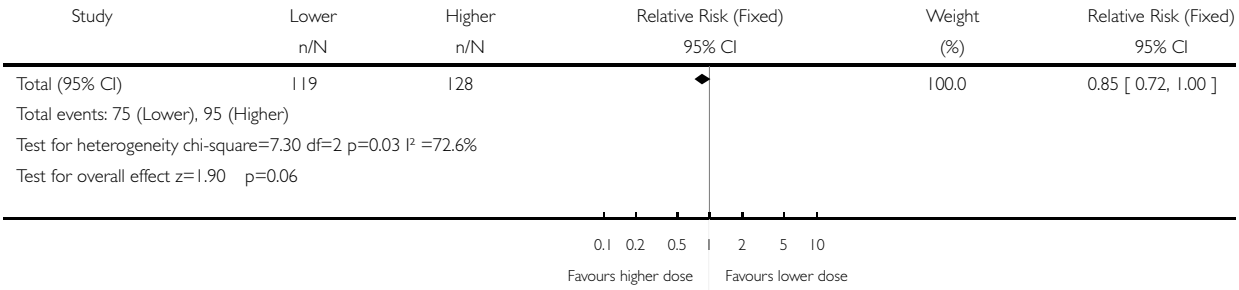
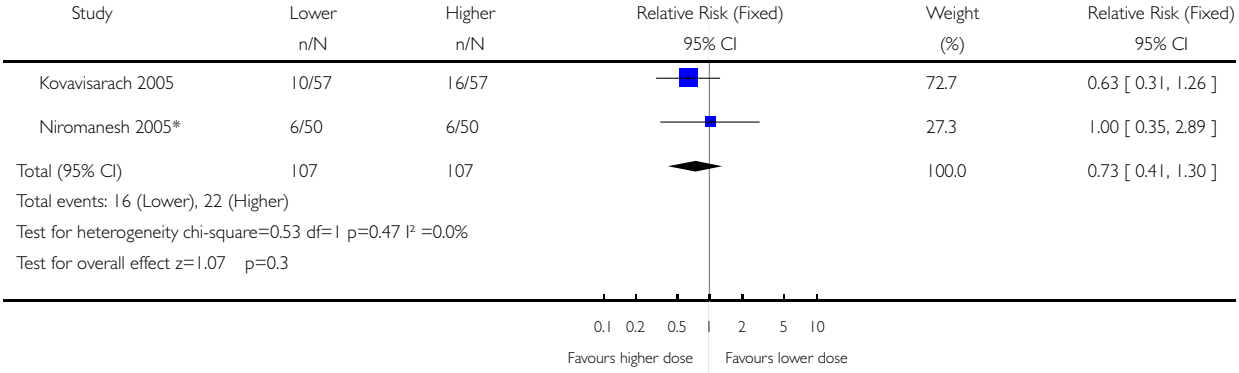


Analysis 05.02. Comparison 05 Vaginal misoprostol lower versus higher dose regimens, Outcome 02 Fever

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

Comparison: 05 Vaginal misoprostol lower versus higher dose regimens

Outcome: 02 Fever

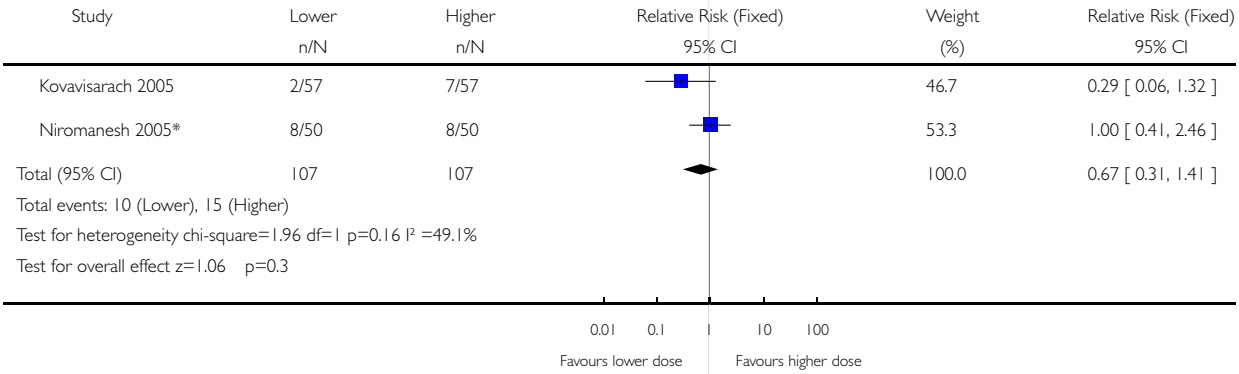


Analysis 05.03. Comparison 05 Vaginal misoprostol lower versus higher dose regimens, Outcome 03 Nausea

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

Comparison: 05 Vaginal misoprostol lower versus higher dose regimens

Outcome: 03 Nausea



Analysis 05.04. Comparison 05 Vaginal misoprostol lower versus higher dose regimens, Outcome 04 Diarrhoea

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

Comparison: 05 Vaginal misoprostol lower versus higher dose regimens

Outcome: 04 Diarrhoea

Study	Lower n/N	Higher n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kovavisarach 2005	0/57	2/57		38.5	0.20 [0.01, 4.08]
Niromanesh 2005*	3/50	4/50		61.5	0.75 [0.18, 3.18]
Total (95% CI)	107	107		100.0	0.54 [0.15, 1.91]
Total events: 3 (Lower), 6 (Higher)					
Test for heterogeneity chi-square=0.62 df=1 p=0.43 I^2 =0.0%					
Test for overall effect z=0.96 p=0.3					

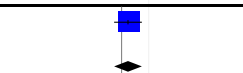
Analysis 06.01. Comparison 06 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 01 Miscarriage < 3 days

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

Comparison: 06 Vaginal misoprostol wet versus dry vaginal preparations

Outcome: 01 Miscarriage < 3 days

Study	Wet n/N	Dry n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gilles 2004	30/41	25/39		100.0	1.14 [0.85, 1.54]
Total (95% CI)	41	39		100.0	1.14 [0.85, 1.54]
Total events: 30 (Wet), 25 (Dry)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.87 p=0.4					



Analysis 06.02. Comparison 06 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 02 Miscarriage < 8 days

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

Comparison: 06 Vaginal misoprostol wet versus dry vaginal preparations

Outcome: 02 Miscarriage < 8 days

Study	Wet n/N	Dry n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gilles 2004	34/41	31/39		100.0	1.04 [0.84, 1.29]
Total (95% CI)	41	39		100.0	1.04 [0.84, 1.29]
Total events: 34 (Wet), 31 (Dry)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.39 p=0.7					

Analysis 06.03. Comparison 06 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 03 Miscarriage < 15 days

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

Comparison: 06 Vaginal misoprostol wet versus dry vaginal preparations

Outcome: 03 Miscarriage < 15 days

Study	Wet n/N	Dry n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gilles 2004	34/41	35/39		100.0	0.92 [0.78, 1.10]
Total (95% CI)	41	39		100.0	0.92 [0.78, 1.10]
Total events: 34 (Wet), 35 (Dry)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.89 p=0.4					

Analysis 06.04. Comparison 06 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 04 Miscarriage < 30 days

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

Comparison: 06 Vaginal misoprostol wet versus dry vaginal preparations

Outcome: 04 Miscarriage < 30 days

Study	Wet n/N	Dry n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gilles 2004	34/41	34/39		100.0	0.95 [0.79, 1.14]
Total (95% CI)	41	39		100.0	0.95 [0.79, 1.14]
Total events: 34 (Wet), 34 (Dry)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.53 p=0.6					

Analysis 06.05. Comparison 06 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 05 Diarrhoea < 48 hours after treatment

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

Comparison: 06 Vaginal misoprostol wet versus dry vaginal preparations

Outcome: 05 Diarrhoea < 48 hours after treatment

Study	Wet n/N	Dry n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gilles 2004	17/40	9/37		100.0	1.75 [0.89, 3.42]
Total (95% CI)	40	37		100.0	1.75 [0.89, 3.42]
Total events: 17 (Wet), 9 (Dry)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.63 p=0.1					

Analysis 06.06. Comparison 06 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 06 Chills < 48 hours of treatment

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

Comparison: 06 Vaginal misoprostol wet versus dry vaginal preparations

Outcome: 06 Chills < 48 hours of treatment

Study	Wet n/N	Dry n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gilles 2004	28/40	19/37		100.0	1.36 [0.94, 1.98]
Total (95% CI)	40	37		100.0	1.36 [0.94, 1.98]
Total events: 28 (Wet), 19 (Dry)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.63 p=0.1					

Analysis 06.07. Comparison 06 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 07 Vomiting < 48 hours of treatment

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

Comparison: 06 Vaginal misoprostol wet versus dry vaginal preparations

Outcome: 07 Vomiting < 48 hours of treatment

Study	Wet n/N	Dry n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gilles 2004	6/40	6/37		100.0	0.93 [0.33, 2.62]
Total (95% CI)	40	37		100.0	0.93 [0.33, 2.62]
Total events: 6 (Wet), 6 (Dry)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.15 p=0.9					

Analysis 06.08. Comparison 06 Vaginal misoprostol wet versus dry vaginal preparations, Outcome 08 Would wish/probably wish same treatment in future nonviable pregnancy

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

Comparison: 06 Vaginal misoprostol wet versus dry vaginal preparations

Outcome: 08 Would wish/probably wish same treatment in future nonviable pregnancy

Study	Wet n/N	Dry n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gilles 2004	31/36	27/37		100.0	1.18 [0.93, 1.49]
Total (95% CI)	36	37		100.0	1.18 [0.93, 1.49]
Total events: 31 (Wet), 27 (Dry)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.38 p=0.2					

Analysis 07.01. Comparison 07 Vaginal misoprostol + methotrexate versus vaginal misoprostol alone, Outcome 01 Miscarriage not complete

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

Comparison: 07 Vaginal misoprostol + methotrexate versus vaginal misoprostol alone

Outcome: 01 Miscarriage not complete

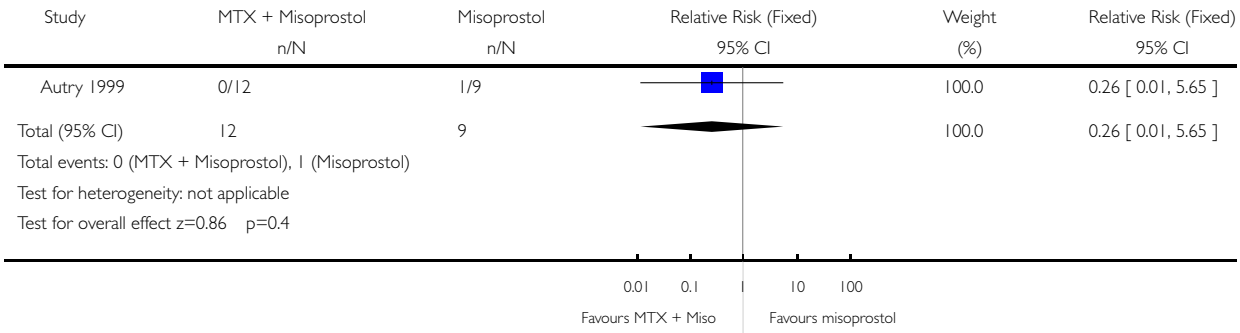
Study	MTX + Misoprostol n/N	Misoprostol n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Autry 1999	0/12	1/9		100.0	0.26 [0.01, 5.65]
Total (95% CI)	12	9		100.0	0.26 [0.01, 5.65]
Total events: 0 (MTX + Misoprostol), 1 (Misoprostol)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.86 p=0.4					

Analysis 07.04. Comparison 07 Vaginal misoprostol + methotrexate versus vaginal misoprostol alone, Outcome 04 Additional surgical evacuation

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

Comparison: 07 Vaginal misoprostol + methotrexate versus vaginal misoprostol alone

Outcome: 04 Additional surgical evacuation

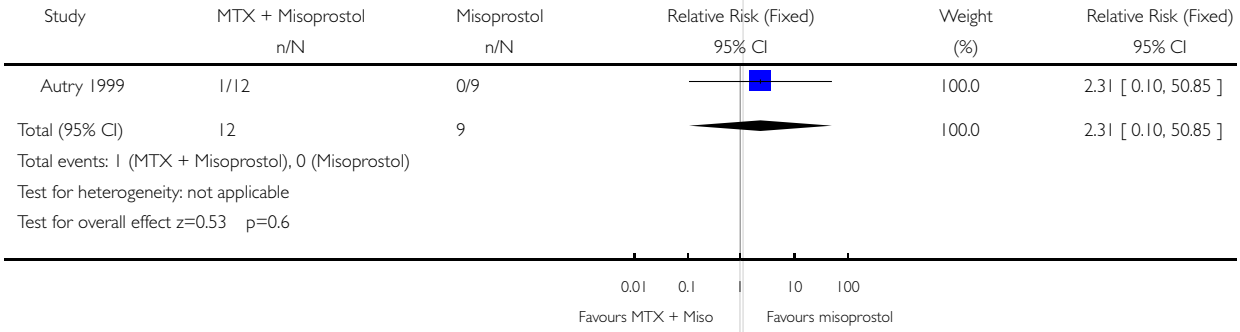


Analysis 07.05. Comparison 07 Vaginal misoprostol + methotrexate versus vaginal misoprostol alone, Outcome 05 Haemorrhage

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

Comparison: 07 Vaginal misoprostol + methotrexate versus vaginal misoprostol alone

Outcome: 05 Haemorrhage



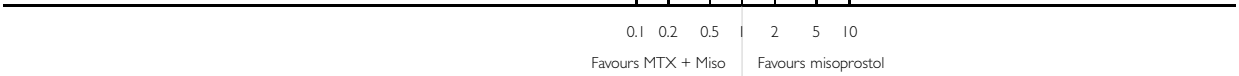
Analysis 07.06. Comparison 07 Vaginal misoprostol + methotrexate versus vaginal misoprostol alone, Outcome 06 Pain relief

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

Comparison: 07 Vaginal misoprostol + methotrexate versus vaginal misoprostol alone

Outcome: 06 Pain relief

Study	MTX + Misoprostol n/N	Misoprostol n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Autry 1999	4/12	4/9		100.0	0.75 [0.25, 2.22]
Total (95% CI)	12	9		100.0	0.75 [0.25, 2.22]
Total events: 4 (MTX + Misoprostol), 4 (Misoprostol)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.52 p=0.6					



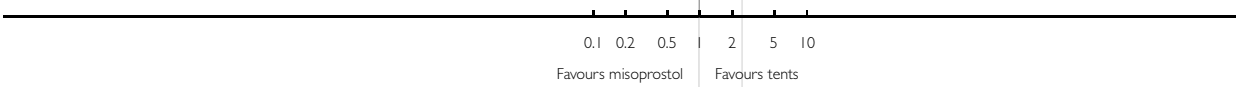
Analysis 08.01. Comparison 08 Vaginal misoprostol plus laminaria tents versus vaginal misoprostol alone, Outcome 01 Miscarriage < 24 hours

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

Comparison: 08 Vaginal misoprostol plus laminaria tents versus vaginal misoprostol alone

Outcome: 01 Miscarriage < 24 hours

Study	Tents n/N	Misoprostol n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Jain 1996*	15/20	15/18		100.0	0.90 [0.65, 1.25]
Total (95% CI)	20	18		100.0	0.90 [0.65, 1.25]
Total events: 15 (Tents), 15 (Misoprostol)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.63 p=0.5					



Analysis 08.02. Comparison 08 Vaginal misoprostol plus laminaria tents versus vaginal misoprostol alone, Outcome 02 Miscarriage < 48 hours

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

Comparison: 08 Vaginal misoprostol plus laminaria tents versus vaginal misoprostol alone

Outcome: 02 Miscarriage < 48 hours

Study	Tents n/N	Misoprostol n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Jain 1996*	19/20	16/18		100.0	1.07 [0.88, 1.29]
Total (95% CI)	20	18		100.0	1.07 [0.88, 1.29]
Total events: 19 (Tents), 16 (Misoprostol)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					

Analysis 09.01. Comparison 09 Oral misoprostol versus vaginal misoprostol, Outcome 01 Complete miscarriage

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

Comparison: 09 Oral misoprostol versus vaginal misoprostol

Outcome: 01 Complete miscarriage

Study	Oral misoprostol n/N	Vaginal misoprostol n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 400 mcg oral misoprostol versus 800 mcg vaginal misoprostol					
Creinin 1997	3/12	7/8		8.4	0.29 [0.10, 0.79]
Subtotal (95% CI)	12	8		8.4	0.29 [0.10, 0.79]
Total events: 3 (Oral misoprostol), 7 (Vaginal misoprostol)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.42 p=0.02					
02 800 mcg oral misoprostol versus 800 mcg vaginal misoprostol					
Ngoc 2004	89/100	91/98		91.6	0.96 [0.88, 1.05]
Subtotal (95% CI)	100	98		91.6	0.96 [0.88, 1.05]
Total events: 89 (Oral misoprostol), 91 (Vaginal misoprostol)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.94 p=0.3					
Total (95% CI)	112	106		100.0	0.90 [0.82, 0.99]
Total events: 92 (Oral misoprostol), 98 (Vaginal misoprostol)					
Test for heterogeneity chi-square=6.75 df=1 p=0.009 I^2 =85.2%					
Test for overall effect z=2.10 p=0.04					

Analysis 09.02. Comparison 09 Oral misoprostol versus vaginal misoprostol, Outcome 02 Vomiting

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

Comparison: 09 Oral misoprostol versus vaginal misoprostol

Outcome: 02 Vomiting

Study	Oral misoprostol n/N	Vaginal misoprostol n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ngoc 2004	4/95	14/95		100.0	0.29 [0.10, 0.84]
Total (95% CI)	95	95		100.0	0.29 [0.10, 0.84]
Total events: 4 (Oral misoprostol), 14 (Vaginal misoprostol)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.29 p=0.02					

Analysis 09.09. Comparison 09 Oral misoprostol versus vaginal misoprostol, Outcome 09 Nausea

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

Comparison: 09 Oral misoprostol versus vaginal misoprostol

Outcome: 09 Nausea

Study	Oral misoprostol n/N	Vaginal misoprostol n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Creinin 1997	6/12	5/8		100.0	0.80 [0.37, 1.74]
Total (95% CI)	12	8		100.0	0.80 [0.37, 1.74]
Total events: 6 (Oral misoprostol), 5 (Vaginal misoprostol)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.56 p=0.6					

Analysis 09.10. Comparison 09 Oral misoprostol versus vaginal misoprostol, Outcome 10 Diarrhoea

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

Comparison: 09 Oral misoprostol versus vaginal misoprostol

Outcome: 10 Diarrhoea

Study	Oral misoprostol n/N	Vaginal misoprostol n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Creinin 1997	5/12	3/8		13.5	1.11 [0.36, 3.40]
Ngoc 2004	24/95	23/95		86.5	1.04 [0.64, 1.71]
Total (95% CI)	107	103		100.0	1.05 [0.67, 1.66]
Total events: 29 (Oral misoprostol), 26 (Vaginal misoprostol)					
Test for heterogeneity chi-square=0.01 df=1 p=0.92 I^2 =0.0%					
Test for overall effect z=0.22 p=0.8					

Analysis 09.12. Comparison 09 Oral misoprostol versus vaginal misoprostol, Outcome 12 Pain (visual analogue scale)

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

Comparison: 09 Oral misoprostol versus vaginal misoprostol

Outcome: 12 Pain (visual analogue scale)

Study	Oral misoprostol N	Mean(SD)	Vaginal misoprostol N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Creinin 1997	11	4.00 (3.60)	7	5.90 (2.70)		100.0	-1.90 [-4.82, 1.02]
Total (95% CI)	11		7			100.0	-1.90 [-4.82, 1.02]
Test for heterogeneity: not applicable							
Test for overall effect z=1.28 p=0.2							

Analysis 09.13. Comparison 09 Oral misoprostol versus vaginal misoprostol, Outcome 13 Fever

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

Comparison: 09 Oral misoprostol versus vaginal misoprostol

Outcome: 13 Fever

Study	Oral misoprostol n/N	Vaginal misoprostol n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ngoc 2004	7/95	7/95		100.0	1.00 [0.36, 2.74]
Total (95% CI)	95	95		100.0	1.00 [0.36, 2.74]

Total events: 7 (Oral misoprostol), 7 (Vaginal misoprostol)

Test for heterogeneity: not applicable

Test for overall effect z=0.00 p=1

Analysis 09.14. Comparison 09 Oral misoprostol versus vaginal misoprostol, Outcome 14 Women's satisfaction with treatment

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

Comparison: 09 Oral misoprostol versus vaginal misoprostol

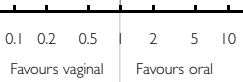
Outcome: 14 Women's satisfaction with treatment

Study	Oral misoprostol n/N	Vaginal misoprostol n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ngoc 2004	86/100	88/98		100.0	0.96 [0.86, 1.06]
Total (95% CI)	100	98		100.0	0.96 [0.86, 1.06]

Total events: 86 (Oral misoprostol), 88 (Vaginal misoprostol)

Test for heterogeneity: not applicable

Test for overall effect z=0.82 p=0.4



Analysis 09.15. Comparison 09 Oral misoprostol versus vaginal misoprostol, Outcome 15 Time to delivery (hours)

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

Comparison: 09 Oral misoprostol versus vaginal misoprostol

Outcome: 15 Time to delivery (hours)

Study	Oral		Vaginal		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Fadalla 2004*	35	14.90 (3.40)	35	10.80 (2.80)		100.0	4.10 [2.64, 5.56]
Total (95% CI)	35		35			100.0	4.10 [2.64, 5.56]
Test for heterogeneity: not applicable							
Test for overall effect z=5.51 p<0.00001							

Analysis 09.16. Comparison 09 Oral misoprostol versus vaginal misoprostol, Outcome 16 Oxytocin infusion

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

Comparison: 09 Oral misoprostol versus vaginal misoprostol

Outcome: 16 Oxytocin infusion

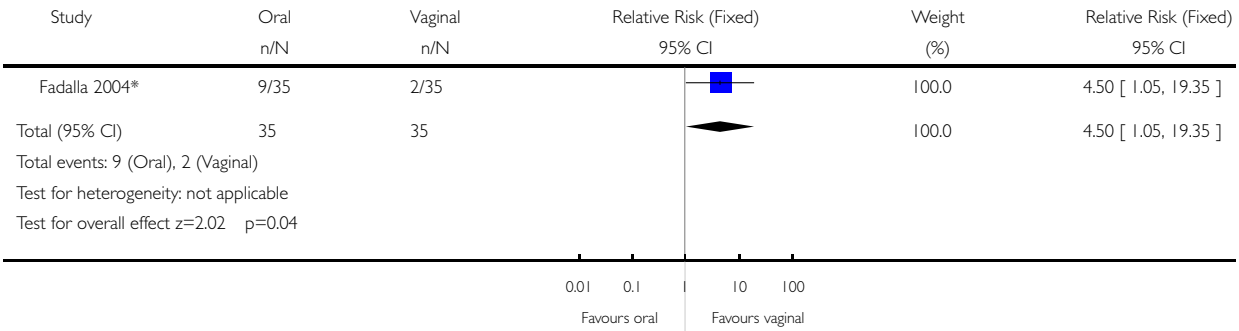
Study	Oral	Vaginal	Relative Risk (Fixed)	Weight	Relative Risk (Fixed)
	n/N	n/N	95% CI	(%)	95% CI
Fadalla 2004*	11/35	4/35		100.0	2.75 [0.97, 7.81]
Total (95% CI)	35	35		100.0	2.75 [0.97, 7.81]
Total events: 11 (Oral), 4 (Vaginal)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.90 p=0.06					

Analysis 09.17. Comparison 09 Oral misoprostol versus vaginal misoprostol, Outcome 17 Manual removal of placenta

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

Comparison: 09 Oral misoprostol versus vaginal misoprostol

Outcome: 17 Manual removal of placenta

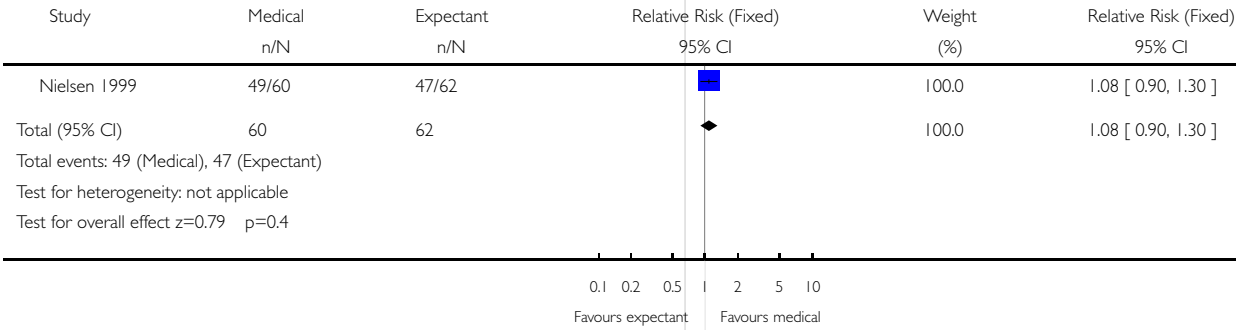


Analysis 10.01. Comparison 10 Oral misoprostol + mifepristone versus expectant management, Outcome 01 Empty uterine cavity at day 5

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

Comparison: 10 Oral misoprostol + mifepristone versus expectant management

Outcome: 01 Empty uterine cavity at day 5

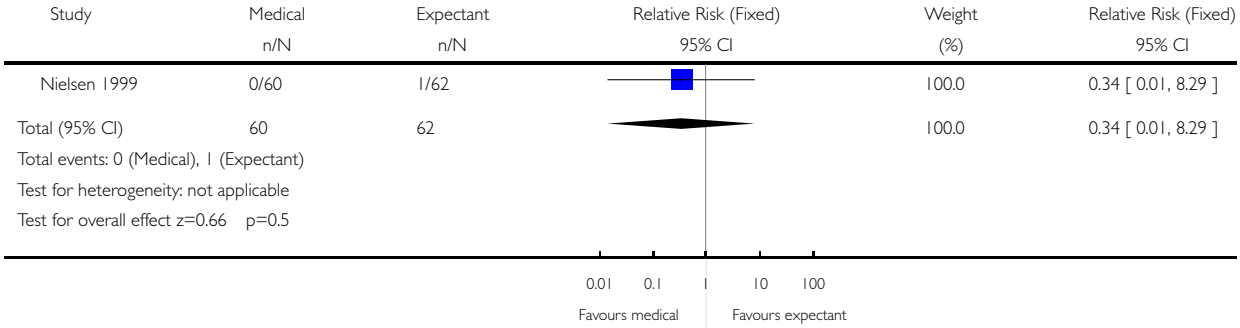


Analysis 10.02. Comparison 10 Oral misoprostol + mifepristone versus expectant management, Outcome 02 Urgent surgical evacuation for bleeding

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

Comparison: 10 Oral misoprostol + mifepristone versus expectant management

Outcome: 02 Urgent surgical evacuation for bleeding

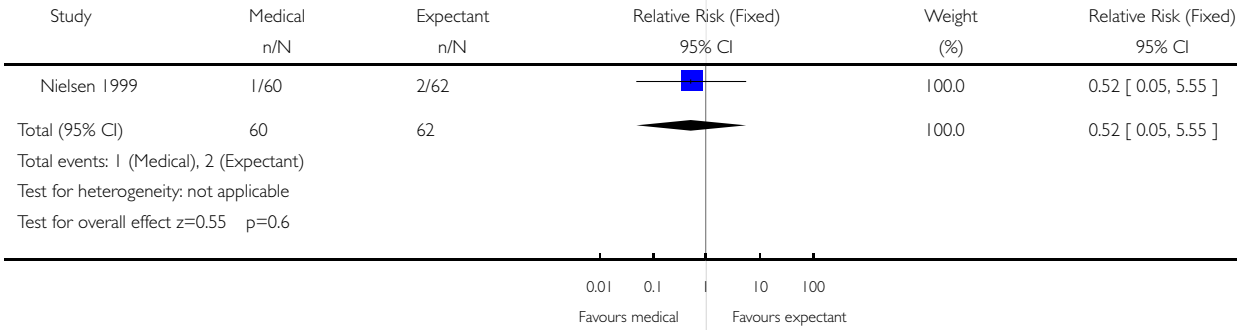


Analysis 10.03. Comparison 10 Oral misoprostol + mifepristone versus expectant management, Outcome 03 Pelvic inflammatory disease

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

Comparison: 10 Oral misoprostol + mifepristone versus expectant management

Outcome: 03 Pelvic inflammatory disease



Analysis 10.04. Comparison 10 Oral misoprostol + mifepristone versus expectant management, Outcome 04 Pain (visual analogue scale day 5)

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

Comparison: 10 Oral misoprostol + mifepristone versus expectant management

Outcome: 04 Pain (visual analogue scale day 5)

Study	Medical N	Medical Mean(SD)	Expectant N	Expectant Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Nielsen 1999	60	66.10 (26.30)	62	62.00 (30.10)		100.0	4.10 [-5.92, 14.12]
Total (95% CI)	60		62			100.0	4.10 [-5.92, 14.12]
Test for heterogeneity: not applicable							
Test for overall effect z=0.80 p=0.4							

Analysis 10.05. Comparison 10 Oral misoprostol + mifepristone versus expectant management, Outcome 05 Sick leave (days)

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

Comparison: 10 Oral misoprostol + mifepristone versus expectant management

Outcome: 05 Sick leave (days)

Study	Medical N	Medical Mean(SD)	Expectant N	Expectant Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Nielsen 1999	60	3.73 (3.80)	62	1.93 (2.70)		100.0	1.80 [0.63, 2.97]
Total (95% CI)	60		62			100.0	1.80 [0.63, 2.97]
Test for heterogeneity: not applicable							
Test for overall effect z=3.01 p=0.003							

Analysis 10.06. Comparison 10 Oral misoprostol + mifepristone versus expectant management, Outcome 06 Bleeding (days)

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

Comparison: 10 Oral misoprostol + mifepristone versus expectant management

Outcome: 06 Bleeding (days)

Study	Medical N	Medical Mean(SD)	Expectant N	Expectant Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Nielsen 1999	60	11.00 (3.26)	62	10.30 (3.11)		100.0	0.70 [-0.43, 1.83]
Total (95% CI)	60		62			100.0	0.70 [-0.43, 1.83]
Test for heterogeneity: not applicable							
Test for overall effect z=1.21 p=0.2							

Analysis 10.07. Comparison 10 Oral misoprostol + mifepristone versus expectant management, Outcome 07 Satisfaction with treatment (visual analogue scale day 14)

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

Comparison: 10 Oral misoprostol + mifepristone versus expectant management

Outcome: 07 Satisfaction with treatment (visual analogue scale day 14)

Study	Medical		Expectant		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Nielsen 1999	60	28.60 (24.80)	62	25.20 (25.60)		100.0	3.40 [-5.54, 12.34]
Total (95% CI)	60		62			100.0	3.40 [-5.54, 12.34]
Test for heterogeneity: not applicable							
Test for overall effect z=0.75 p=0.5							

Analysis 11.01. Comparison 11 Sublingual misoprostol versus vaginal misoprostol, Outcome 01 Complete miscarriage

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

Comparison: 11 Sublingual misoprostol versus vaginal misoprostol

Outcome: 01 Complete miscarriage

Study	Sublingual	Vaginal	Relative Risk (Fixed)	Weight	Relative Risk (Fixed)
	n/N	n/N	95% CI	(%)	95% CI
Tang 2003	35/40	35/40		100.0	1.00 [0.85, 1.18]
Total (95% CI)	40	40		100.0	1.00 [0.85, 1.18]
Total events: 35 (Sublingual), 35 (Vaginal)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					

Analysis 11.02. Comparison 11 Sublingual misoprostol versus vaginal misoprostol, Outcome 02 Nausea

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

Comparison: 11 Sublingual misoprostol versus vaginal misoprostol

Outcome: 02 Nausea

Study	Sublingual n/N	Vaginal n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tang 2003	24/40	20/40		100.0	1.20 [0.80, 1.79]
Total (95% CI)	40	40		100.0	1.20 [0.80, 1.79]
Total events: 24 (Sublingual), 20 (Vaginal)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.89 p=0.4					

Analysis 11.03. Comparison 11 Sublingual misoprostol versus vaginal misoprostol, Outcome 03 Vomiting

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

Comparison: 11 Sublingual misoprostol versus vaginal misoprostol

Outcome: 03 Vomiting

Study	Sublingual n/N	Vaginal n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tang 2003	7/40	9/40		100.0	0.78 [0.32, 1.88]
Total (95% CI)	40	40		100.0	0.78 [0.32, 1.88]
Total events: 7 (Sublingual), 9 (Vaginal)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.56 p=0.6					

Analysis 11.04. Comparison 11 Sublingual misoprostol versus vaginal misoprostol, Outcome 04 Diarrhoea

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

Comparison: 11 Sublingual misoprostol versus vaginal misoprostol

Outcome: 04 Diarrhoea

Study	Sublingual n/N	Vaginal n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tang 2003	28/40	11/40		100.0	2.55 [1.48, 4.38]
Total (95% CI)	40	40		100.0	2.55 [1.48, 4.38]
Total events: 28 (Sublingual), 11 (Vaginal)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.38 p=0.0007					

Analysis 11.05. Comparison 11 Sublingual misoprostol versus vaginal misoprostol, Outcome 05 Haemoglobin day 43

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

Comparison: 11 Sublingual misoprostol versus vaginal misoprostol

Outcome: 05 Haemoglobin day 43

Study	Sublingual N	Mean(SD)	Vaginal N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Tang 2003	40	12.60 (1.10)	40	12.50 (1.10)		100.0	0.10 [-0.38, 0.58]
Total (95% CI)	40		40			100.0	0.10 [-0.38, 0.58]
Test for heterogeneity: not applicable							
Test for overall effect z=0.41 p=0.7							

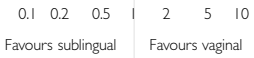
Analysis 11.06. Comparison 11 Sublingual misoprostol versus vaginal misoprostol, Outcome 06 Intolerable pain

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

Comparison: 11 Sublingual misoprostol versus vaginal misoprostol

Outcome: 06 Intolerable pain

Study	Sublingual n/N	Vaginal n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tang 2003	6/40	8/40		100.0	0.75 [0.29, 1.97]
Total (95% CI)	40	40		100.0	0.75 [0.29, 1.97]
Total events: 6 (Sublingual), 8 (Vaginal)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.59 p=0.6					



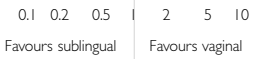
Analysis 11.07. Comparison 11 Sublingual misoprostol versus vaginal misoprostol, Outcome 07 Satisfied with treatment

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

Comparison: 11 Sublingual misoprostol versus vaginal misoprostol

Outcome: 07 Satisfied with treatment

Study	Sublingual n/N	Vaginal n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tang 2003	30/38	31/39		100.0	0.99 [0.79, 1.25]
Total (95% CI)	38	39		100.0	0.99 [0.79, 1.25]
Total events: 30 (Sublingual), 31 (Vaginal)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.06 p=1					



Analysis 12.01. Comparison 12 Mifepristone versus placebo, Outcome 01 Miscarriage < 48 hours

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

Comparison: 12 Mifepristone versus placebo

Outcome: 01 Miscarriage < 48 hours

Study	Mifepristone n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lelaidier 1993	2/23	0/23		100.0	5.00 [0.25, 98.75]
Total (95% CI)	23	23		100.0	5.00 [0.25, 98.75]
Total events: 2 (Mifepristone), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.06 p=0.3					

Analysis 12.02. Comparison 12 Mifepristone versus placebo, Outcome 02 Miscarriage < 3 days

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

Comparison: 12 Mifepristone versus placebo

Outcome: 02 Miscarriage < 3 days

Study	Mifepristone n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lelaidier 1993	9/23	0/23		100.0	19.00 [1.17, 308.40]
Total (95% CI)	23	23		100.0	19.00 [1.17, 308.40]
Total events: 9 (Mifepristone), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.07 p=0.04					

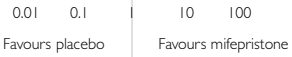
Analysis 12.03. Comparison 12 Mifepristone versus placebo, Outcome 03 Miscarriage < 4 days

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

Comparison: 12 Mifepristone versus placebo

Outcome: 03 Miscarriage < 4 days

Study	Mifepristone n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lelaidier 1993	14/23	1/23		100.0	14.00 [2.00, 97.88]
Total (95% CI)	23	23		100.0	14.00 [2.00, 97.88]
Total events: 14 (Mifepristone), 1 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.66 p=0.008					



Analysis 12.04. Comparison 12 Mifepristone versus placebo, Outcome 04 Miscarriage < 5 days

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

Comparison: 12 Mifepristone versus placebo

Outcome: 04 Miscarriage < 5 days

Study	Mifepristone n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lelaidier 1993	19/23	2/23		100.0	9.50 [2.49, 36.19]
Total (95% CI)	23	23		100.0	9.50 [2.49, 36.19]
Total events: 19 (Mifepristone), 2 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.30 p=0.001					

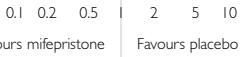
Analysis 12.05. Comparison 12 Mifepristone versus placebo, Outcome 05 Vaginal bleeding before day 5

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

Comparison: 12 Mifepristone versus placebo

Outcome: 05 Vaginal bleeding before day 5

Study	Mifepristone n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lelaidier 1993	23/23	5/21		100.0	4.20 [1.95, 9.03]
Total (95% CI)	23	21		100.0	4.20 [1.95, 9.03]
Total events: 23 (Mifepristone), 5 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.68 p=0.0002					



Analysis 12.06. Comparison 12 Mifepristone versus placebo, Outcome 06 Pain before day 5

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

Comparison: 12 Mifepristone versus placebo

Outcome: 06 Pain before day 5

Study	Mifepristone n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lelaidier 1993	12/23	5/21		100.0	2.19 [0.93, 5.17]
Total (95% CI)	23	21		100.0	2.19 [0.93, 5.17]
Total events: 12 (Mifepristone), 5 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.79 p=0.07					

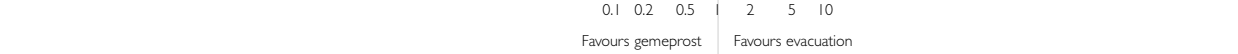
Analysis 13.01. Comparison 13 Vaginal gemeprost versus surgical evacuation of uterus, Outcome 01 Surgical evacuation

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

Comparison: 13 Vaginal gemeprost versus surgical evacuation of uterus

Outcome: 01 Surgical evacuation

Study	Gemeprost n/N	Evacuation n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Egarter 1995	10/43	44/44		100.0	0.23 [0.14, 0.40]
Total (95% CI)	43	44		100.0	0.23 [0.14, 0.40]
Total events: 10 (Gemeprost), 44 (Evacuation)					
Test for heterogeneity: not applicable					
Test for overall effect z=5.27 p<0.00001					



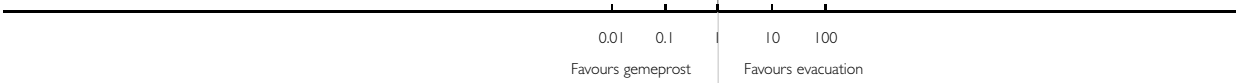
Analysis 13.02. Comparison 13 Vaginal gemeprost versus surgical evacuation of uterus, Outcome 02 Perforation of uterus

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

Comparison: 13 Vaginal gemeprost versus surgical evacuation of uterus

Outcome: 02 Perforation of uterus

Study	Gemeprost n/N	Evacuation n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Egarter 1995	0/43	2/44		100.0	0.20 [0.01, 4.14]
Total (95% CI)	43	44		100.0	0.20 [0.01, 4.14]
Total events: 0 (Gemeprost), 2 (Evacuation)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.03 p=0.3					



Analysis 13.03. Comparison 13 Vaginal gemeprost versus surgical evacuation of uterus, Outcome 03 Nausea

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

Comparison: 13 Vaginal gemeprost versus surgical evacuation of uterus

Outcome: 03 Nausea