Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death (Review)

Dodd JM, Crowther CA

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TABLE OF CONTENTS

[Intervention Review]

Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Jodie M Dodd[1], Caroline A Crowther[2]

[1]School of Paediatrics and Reproductive Health, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia. [2]ARCH: Australian Research Centre for Health of Women and Babies, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia

Contact address: Jodie M Dodd, School of Paediatrics and Reproductive Health, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Women's and Children's Hospital, 72 King William Road, Adelaide, South Australia, 5006, Australia. jodie.dodd@adelaide.edu.au.

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ABSTRACT

Background

A woman may need to give birth prior to the spontaneous onset of labour in situations where the fetus has died in utero (also called a stillbirth), or for the termination of pregnancy where the fetus, if born alive would not survive or would have a permanent handicap. Misoprostol is a prostaglandin medication that can be used to induce labour in these situations.

Objectives

To compare the benefits and harms of misoprostol to induce labour to terminate pregnancy in the second and third trimester for women with a fetal anomaly or after intrauterine fetal death when compared with other methods of induction of labour.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (November 2009).

Selection criteria

Randomised controlled trials comparing misoprostol with placebo or no treatment, or any other method of induction of labour, for women undergoing induction of labour to terminate pregnancy in the second and third trimester following an intrauterine fetal death or for fetal anomalies.

Data collection and analysis

Both authors independently assessed trial quality and extracted data.

Main results

We included 38 studies (3679 women).

Nine studies included pregnancies after intrauterine deaths, five studies included termination of pregnancies because of fetal anomalies when the fetus was still alive and the rest (24) presented the pooled data for intrauterine deaths, fetal anomalies and social reasons.

When compared with agents that have traditionally been used to induce labour in this setting (for example, gemeprost, prostaglandin E_2 and prostaglandin F_{2alpha}), vaginal misoprostol is as effective in ensuring vaginal birth within 24 hours, with a similar induction to birth interval. Vaginal misoprostol is associated with a reduction in the occurrence of maternal gastrointestinal side effects such as nausea, vomiting and diarrhoea when compared with other prostaglandin preparations. While the different treatments involving various prostaglandin preparations appear comparable for the reported outcomes, the information available regarding rare maternal complications, such as uterine rupture, is limited.

Authors' conclusions

The use of vaginal misoprostol in the termination of second and third trimester of pregnancy is as effective as other prostaglandin preparations (including cervagem, prostaglandin E_2 and prostaglandin F_{2alpha}), and more effective than oral administration of misoprostol. However, important information regarding maternal safety, and in particular the occurrence of rare outcomes such as uterine rupture, remains limited. Future research efforts should be directed towards determining the optimal dose and frequency of administration, with particular attention to standardised reporting of all relevant outcomes and assessment of rare adverse events. Further information is required about the use of sublingual misoprostol in this setting.

PLAIN LANGUAGE SUMMARY

Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or following intrauterine fetal death

A woman may need to give birth prior to the spontaneous onset of labour in middle to late pregnancy to terminate the pregnancy in situations where the fetus, if born alive, would not survive or would have permanent handicaps, or where the fetus has died in utero (also called a stillbirth). Misoprostol is a prostaglandin medication that can be used to induce labour in these situations. This review included 38 randomised controlled studies, involving 3679 women. Vaginal misoprostol was as effective as other agents in inducing labour and achieving vaginal birth within 24 hours, with a reduction in the occurrence of maternal side effects. Side effects include gastrointestinal disturbance (nausea, vomiting, diarrhoea). The information on rare adverse events (including uterine rupture) is limited.

BACKGROUND

Description of the condition

A woman may need to give birth prior to the spontaneous onset of labour in situations where the fetus has died in utero (also called a stillbirth), or for the termination of pregnancy where the fetus, if born alive, would not survive or would have significant disability. This situation is psychologically stressful for the woman, her partner and family, and for the health professionals caring for her.

When a baby dies before birth, the options for care are either to wait for labour to start spontaneously or to induce labour. Most women (over 90%) begin to contract and labour within three weeks of their baby dying, but if labour does not begin, there is a risk of developing a disseminated intravascular coagulopathy (DIC) (Weiner 1999). This complication develops when various factors in the blood which usually stop a person from bleeding (clotting factors) are used faster than they can be replaced. This increases the risk of severe bleeding complications or haemorrhage. A disadvantage of a long interval between fetal death and birth relates to the degree of information that can be obtained from a postmortem examination or autopsy of the baby. Where there has been a considerable delay between the death of the baby and birth, the tissue may begin to break down, limiting the amount of information that can be obtained about the cause of death (Weiner

1999). This may have implications for counselling about the risks for any future pregnancy.

Description of the intervention

Inducing labour may involve the use of the hormone oxytocin which causes the uterus to contract (Kelly 2001). When labour is induced early in pregnancy, this has been associated with long and painful labours, as the uterus is less sensitive to oxytocin before term (Weiner 1999). Prostaglandins have been used to induce labour and are particularly useful where a woman's cervix is unfavourable or not ready to commence labour (Mackenzie 1999). Prostaglandins have been administered orally (French 2001), vaginally (Kelly 2003), into the cervix (intracervical), outside the amniotic sac (extra-amniotically) (Hutton 2001), or intravenously (Luckas 2000). There are also mechanical devices which have been developed to dilate or open the cervix (Boulvain 2001).

How the intervention might work

Misoprostol is a synthetic prostaglandin that is structurally related to prostaglandin E_1 (PGE_1). Misoprostol is licensed for use as an anti-ulcer medication in the treatment of gastric ulcer disease and does not have a product license for use in pregnancy anywhere in the world. Despite this, the use of misoprostol in obstetric and gynaecological practice has increased, being used widely in the management of first and second trimester abortion (Dickinson 1998), and in the third trimester of pregnancy following intrauterine fetal death (Mariani-Neto 1987). More recently, misoprostol has been used in the induction of labour at term in the presence of a viable fetus, with both vaginal (Hofmeyr 2003) and oral (Alfirevic 2006) routes of administration being used. Misoprostol has been investigated for use in the third stage of labour to prevent postpartum haemorrhage (Gulmezoglu 2007). Potential advantages to the use of misoprostol over other prostaglandin preparations include its stability at room temperature (other prostaglandins need to be stored in the refrigerator) and low cost. This has important implications for women in low-resource countries.

The Cochrane reviews assessing misoprostol for the induction of labour at term in the presence of a live fetus (Alfirevic 2006; Hofmeyr 2003) concluded that there was considerable variation in both the dose and frequency of misoprostol administered to induce labour, and that at present the optimal dosing regimen is uncertain. There have been calls to further investigate the lowest effective dose of misoprostol, thereby minimising side effects and maximising safety for both the woman and her infant (Alfirevic 2006; Hofmeyr 2003).

Why it is important to do this review

The issues related to the use of low doses of misoprostol are a little different for women who are having labour induced to terminate their pregnancy because of fetal anomalies or after intrauterine fetal death. While side effects (including uterine hyperstimulation, nausea, vomiting, and diarrhoea) and safety (particularly rare complications such as uterine rupture) are important considerations for the woman, issues related to fetal wellbeing are not. Furthermore, it is necessary to consider the receptivity of the uterus to prostaglandin medication, especially at early gestational ages, where the use of low doses of misoprostol may be ineffective in inducing labour, or be associated with a long induction to delivery interval. Sensitivity of the uterus to medication may also be influenced by whether or not the fetus is alive at the time of induction. The aim of this review is to assess the benefits and harms of misoprostol to induce labour after the death in utero of a fetus, or for fetal anomalies in the second or third trimester of pregnancy when compared with other methods of induction of labour.

Clinical trials of medical treatment, including misoprostol, for fetal deaths before 24 weeks are considered in a separate Cochrane review (Neilson 2006).

In addition, there is a published Cochrane protocol planning to review trials of medical treatments, including misoprostol, for mid-trimester termination of pregnancy (Medema 2005).

OBJECTIVES

To compare, using the best available evidence, the benefits and harms of misoprostol to induce labour to terminate pregnancy in the second and third trimester for women with a fetal anomaly or after intrauterine fetal death when compared with other methods of induction of labour.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished, and ongoing randomised controlled trials comparing misoprostol (either oral or vaginal administration) with placebo or no treatment, or any other method of induction of labour (including prostaglandins administered orally, vaginally, intracervically, extra-amniotically; oxytocin; misoprostol (oral or vaginal); mifepristone; or mechanical methods of induction including extra-amniotic Foley catheter or laminaria).

We excluded quasi-randomised trials (e.g. those randomised by date of birth or hospital number). We have included studies reported only in abstract form in the 'Studies awaiting classification'

category, and will include these in analyses when published as full reports.

Types of participants

Women undergoing induction of labour to terminate pregnancy in the second and third trimester following an intrauterine fetal death or for fetal anomalies. Where trials included a mix of indications for termination of pregnancy (including social reasons), they were eligible for inclusion if less than 30% of participants were undergoing termination of pregnancy for social indications, or where information was reported separately by indication.

Types of interventions

Misoprostol for the induction of labour to terminate pregnancy versus placebo or no treatment, or any other method of induction of labour to terminate pregnancy in the second and third trimester. We have included studies reporting comparisons between different routes of administration or different doses of misoprostol.

Types of outcome measures

Primary outcomes

1. Vaginal birth not achieved within 24 hours
2. Induction to delivery interval

Secondary outcomes

1. Analgesia requirements (as defined by trial authors)
2. Blood loss (as defined by trial authors)
3. Need for blood transfusion
4. Surgical evacuation of the uterus (as defined by trial authors)
5. Puerperal sepsis requiring antibiotic treatment
6. Maternal death or serious maternal morbidity (e.g. admission to intensive care unit; uterine rupture)
7. Side effects - all
8. Side effects - nausea
9. Side effects - vomiting
10. Side effects - diarrhoea
11. Side effects - other
12. Psychological wellbeing of the woman (as defined by trial authors)
13. Maternal satisfaction with induction process

Only outcomes with available data appear in the analysis table. Outcome data that were not prestated by the review authors, but reported by the authors, are labelled as such in the analysis.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (November 2009).

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. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

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 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Both review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third person.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person. We entered data into Review Manager software (RevMan 2008) and checked for accuracy.

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

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We resolved any disagreement by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

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

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear.

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

We described for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or was supplied by the trial authors, we re-included missing data in the analyses. We assessed methods as:

- adequate (defined as less than 20% incomplete data);
- inadequate:
- unclear.

(5) Selective reporting bias

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

- adequate (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We have described for each included study any important concerns we have about other possible sources of bias, including study design, early stopping of the trial due to data-dependent processes or extreme baseline imbalance.
We assessed whether each study was free of other problems that could put it at risk of bias as:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2008). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We explored the impact of the level of bias through undertaking Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference if outcomes are measured in the same way between trials. We used the standardised mean difference to combine trials that measured the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We did not identify any eligible cluster-randomised trials.

Crossover trials

Crossover trials are not considered an appropriate study design to evaluate this intervention.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data (considered to be more than 20%) in the overall assessment of treatment effect by using sensitivity analysis.

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

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. Where we identified substantial heterogeneity (above 50%), we have explored it by pre-specified subgroup analysis.

Assessment of reporting biases

Where we suspect reporting bias (*see* 'Selective reporting bias' above), we have attempted to contact study authors asking them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we have explored the impact of including such studies in the overall assessment of results by a Sensitivity analysis.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect inverse variance meta-analysis for combining data where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Where we suspected clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we used random-effects meta-analysis.

If we identified substantial heterogeneity in a fixed-effect meta-analysis, we have noted this and repeated the analysis using a random-effects method.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses:

1. oral versus vaginal route of administration of misoprostol;
2. dose of misoprostol used;
3. indication for induction of labour (that is intrauterine fetal death versus termination of live pregnancy); and
4. gestational age (second versus third trimester of pregnancy as defined by trial authors);
5. maternal parity; and
6. previous caesarean section.

We used the following primary outcomes in subgroup analysis:

- vaginal birth not achieved within 24 hours;
- induction to delivery interval.

For fixed-effect meta-analyses, we conducted planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. For random-effects meta-analyses, we assessed differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We did not conduct sensitivity analyses.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

Our search strategy identified 54 studies for consideration, of which we included 38 (involving 3679 women), excluded 11 studies and five studies are awaiting classification.

Included studies

Thirty-eight studies (involving 3490 women) met our inclusion criteria. The interventions compared included:

- vaginal misoprostol compared with oral misoprostol (Akoury 2004; Bebbington 2002; Behrashi 2008; Caliskan 2005; Chittacharoen 2003; Dickinson 2003; Elhassan 2008; Fadalla 2004; Gilbert 2001; Neto 1988; Nyende 2004);
- vaginal misoprostol compared with vaginal gemeprost (alone or with oxytocin) (Dickinson 1998; Nor Azlin 2006; Nuutila 1997);
- vaginal misoprostol compared with vaginal prostaglandin E2 (alone or with other agents) (Herabutya 1997; Jain 1999; Kara 1999; Makhlouf 2003; Owen 1999);
- vaginal misoprostol compared with prostaglandin F2alpha (Akoury 2004; Ghorab 1998; Munthali 2001; Perry 1999; Su 2005; Zuo 1998);
- vaginal misoprostol compared with oxytocin alone (Nakintu 2001);
- vaginal misoprostol alone compared with vaginal misoprostol and oxytocin (Hidar 2001);
- vaginal misoprostol compared with vaginal glyceryl trinitrate (Makhlouf 2003);
- vaginal misoprostol alone compared with vaginal misoprostol and laminaria (Jain 1994);
- vaginal misoprostol alone compared with vaginal misoprostol and nitric oxide donor (Hidar 2005);
- oral misoprostol compared with prostaglandin F2alpha (Akoury 2004);
- combination of oral and vaginal misoprostol compared with vaginal misoprostol alone (Dickinson 2003; Feldman 2003), oral misoprostol alone (Dickinson 2003), and dilation and evacuation (Grimes 2005);
- sublingual misoprostol compared with vaginal misoprostol (Caliskan 2005; Elhassan 2008);
- sublingual misoprostol compared with oral misoprostol (Caliskan 2005; Elhassan 2008); and two different doses of sublingual misoprostol (Caliskan 2009).

Dose and route of administration

There were several trials comparing a dosing interval of six hours with 12 hours (Herabutya 2005; Jain 1996; Nuutila 1997), and several trials comparing varying doses of vaginal misoprostol. These were arbitrarily divided into those comparing a low dose (less than 800 mcg in a 24-hour period) with a moderate dose (between 800 mcg and 2400 mcg in a 24-hour period) (Dickinson 2002; Niromanesh 2005), and those comparing a moderate dose (800 mcg to 2400 mcg in a 24-hour period) with a high dose (in excess of 2400 mcg in a 24-hour period) (Pongsatha 2004). The route of administration of misoprostol (vaginal, oral or combined oral and vaginal) varied considerably across trials, as did the dose used (a cumulative dose in 24 hours ranging from 400 mcg to 3200 mcg) and the dosing interval administered (from three-hourly intervals to 12-hourly intervals).

Participant population

Most trials recruited women undergoing termination of pregnancy in the presence of both a live fetus, and following intrauterine fetal death, with no separate reporting of outcomes by method of induction of labour and indication for induction.

Reported outcomes

There was variable reporting of the prespecified outcomes, with the majority of trials only reporting vaginal birth not achieved in 24 hours, induction to birth interval (often as a median and interquartile range precluding inclusion in the meta-analysis), surgical evacuation of the uterus, and side effects from therapy. More severe but less common complications (including excessive blood loss, need for transfusion, and complications such as uterine rupture) were poorly reported. Maternal satisfaction with the process of induction of labour was reported in several trials, but reported as a median and interquartile range, precluding inclusion in the meta-analysis.

For further details *see* Characteristics of included studies.

Excluded studies

We excluded 11 trials. Six trials involved only women undergoing termination of pregnancy for 'social' indications (Biswas 2007; El-Refaey 1995; Guix 2005; Marquette 2005; Nigam 2006; Saha 2006); and three trials used quasi-randomisation methods (Eng 1997; Herabutya 2001; Yapar 1996). In one trial, termination of pregnancy was effected in all women using the same misoprostol regimen, with randomisation occurring to administration on an inpatient versus outpatient basis (Gonzalez 2001). One trial involved women at seven to 12 weeks' gestation with early pregnancy failure (Ayudhaya 2006). For further details *see* Characteristics of excluded studies.

Studies awaiting classification

Five trials have been presented only in abstract form; we will assess these once further details are obtained (Abdel Fattah 1997; Agrawal 2006; Nuthalapaty 2004; Roy 2003; Surita 1997). For further details *see* Characteristics of studies awaiting classification.

Risk of bias in included studies

The overall quality of the included trials varied from good to fair. All trials were stated to be randomised, and while most utilised a random number table to generate the randomisation sequence, the method of randomisation was unclear in 13 of the trials (Behrashi

2008; Elhassan 2008; Fadalla 2004; Ghorab 1998; Herabutya 1997; Hidar 2005; Jain 1996; Kara 1999; Neto 1988; Niromanesh 2005; Nor Azlin 2006; Nyende 2004; Pongsatha 2004). Allocation concealment involved the use of sealed opaque envelopes in the majority of trials, but was considered to be unclear in 19 of the trials (Behrashi 2008; Caliskan 2005; Elhassan 2008; Fadalla 2004; Gilbert 2001; Ghorab 1998; Herabutya 1997; Hidar 2005; Jain 1994; Jain 1996; Jain 1999; Kara 1999; Makhlouf 2003; Nakintu 2001; Neto 1988; Niromanesh 2005; Nyende 2004; Pongsatha 2004; Zuo 1998). Blinding of women and outcome assessors was achieved in only one trial (Dickinson 1998), with women, caregivers and outcome assessors aware of the treatment allocated in all of the remaining trials. Four trials were stopped prior to reaching the projected sample size following an interim analysis of results (Dickinson 1998; Dickinson 2003; Gilbert 2001; Owen 1999), and one trial was stopped prior to reaching sample size due to difficulties with recruitment (Grimes 2005).
Refer to table Characteristics of included studies for further details.

Effects of interventions

Vaginal misoprostol versus oral misoprostol (Analysis 1)

We included 11 studies involving 855 women. Women administered vaginal misoprostol were more likely to achieve vaginal birth within 24 hours (risk ratio (RR) 0.18, 95% confidence interval (CI) 0.04 to 0.78; I^2 = 77%; random-effects model (six studies, 507 women)) and had a shorter mean induction to birth interval (mean difference (MD) -5.54 hours, 95% CI -8.92 to -2.16; I^2 = 87%; random-effects model (eight studies, 590 women)) when compared with women administered oral misoprostol. The test for heterogeneity was significant for these outcomes, possibly accounted for by the Chittacharoen 2003 trial, in which a much higher dose of oral misoprostol was used than in the other trials. There were no statistically significant differences for the other outcomes reported including need for analgesia, surgical evacuation of the uterus, and side effects including nausea, vomiting, diarrhoea and pyrexia.

Vaginal misoprostol six-hourly dosing intervals versus 12-hourly dosing intervals (Analysis 2)

We included three studies involving 416 women. There were no statistically significant differences identified between the dosing regimens for the outcomes vaginal birth not achieved in 24 hours or the mean induction to birth interval. However, the six-hourly dosing interval was associated with an increase in women's experience of side effects, particularly vomiting (RR 2.26, 95% CI 1.09 to 4.71 (three studies, 416 women)).

Vaginal misoprostol versus Gemeprost (alone or with oxytocin) (Analysis 3)

We included four studies involving 315 women. There were no statistically significant differences identified between the two agents for the outcomes vaginal birth not achieved in 24 hours, mean induction to delivery interval, analgesic requirements, blood loss, or experience of side effects, although the outcome pyrexia was of borderline statistical significance (RR 0.38, 95% CI 0.13 to 1.06 (two studies, 154 women)). However, there was statistical heterogeneity identified, possibly accounted for by the low dose of misoprostol used in the trial by Nuutila (Nuutila 1997).

Vaginal misoprostol versus prostaglandin E_2 (alone or with other agents) (Analysis 4)

We included six studies involving 410 women. There were no statistically significant differences in a woman's chance of achieving vaginal birth within 24 hours (RR 0.62, 95% CI 0.36 to 1.04), or in their mean induction to birth interval (MD -1.71 hours, 95% CI -10.05 to 6.63; I^2 = 83%; random-effects (four studies, 165 women)). Women administered misoprostol were less likely to experience any side effects (RR 1.59, 95% CI 1.05 to 2.40 (one study, 80 women)), to experience nausea (RR 0.59, 95% CI 0.35 to 0.99 (one study, 126 women)), or diarrhoea (RR 0.20, 95% CI 0.06 to 0.67 (three studies, 261 women)) when compared with women administered prostaglandin E_2.

Vaginal misoprostol versus prostaglandin F_{2alpha} (Analysis 5)

We included six studies involving 534 women. When compared with prostaglandin F_{2alpha}, vaginal misoprostol was not associated with a statistically significant difference in a woman's chance of achieving vaginal birth within 24 hours (RR 1.07, 95% CI 0.28 to 4.06; I^2 = 70%, random-effects (three studies, 213 women) or in the mean induction to birth interval (MD -2.84, 95% CI -6.06 to 0.38; I^2 = 71%, random-effects (four studies, 378 women)). Women administered vaginal misoprostol were less likely to require surgical evacuation of the uterus (RR 0.63, 95% CI 0.41 to 0.98 (five studies, 439 women)), and less likely to experience both nausea (RR 0.67, 95% CI 0.47 to 0.95 (three studies, 338 women)) and vomiting (RR 0.61, 95% CI 0.42 to 0.89 (four studies, 378 women)).

Vaginal misoprostol versus vaginal misoprostol and oxytocin (Analysis 6)

We identified a single trial of 76 women, with no statistically significant differences reported for the outcomes: mean induction to birth interval; surgical evacuation of the uterus; side effects; vomiting; diarrhoea; or pyrexia.

Vaginal misoprostol versus vaginal glyceryl tri-nitrate (Analysis 7)

We identified a single trial of 100 women, in which no primary outcomes were reported. Women who were administered vaginal misoprostol were more likely to require analgesia (RR 2.22, 95% CI 1.12 to 4.40 (one study, 100 women)), and to experience any side effects (RR 75.00, 95% CI 4.73 to 1188.78), including vomiting (RR 35.00, 95% CI 2.16 to 566.54) and pyrexia (RR 31.00, 95% CI 1.91 to 504.35) when compared with women administered vaginal glyceryl tri-nitrate.

Vaginal misoprostol versus vaginal misoprostol and laminaria (Analysis 8)

We identified a single trial of 68 women. There were no statistically significant differences identified between the two methods of induction for the following outcomes: vaginal birth not achieved in 24 hours; blood loss greater than 500 mL; need for transfusion; and side effects (vomiting, diarrhoea, and pyrexia).

Vaginal misoprostol versus vaginal misoprostol and vaginal nitric oxide donor (Analysis 9)

We identified a single trial involving 61 women, with no statistically significant differences reported for the following outcomes: vaginal birth not achieved in 24 hours; mean induction to birth interval; and any side effects.

Oral misoprostol versus prostaglandin F_{2alpha} (Analysis 10)

We identified a single trial involving 133 women. Women who were administered oral misoprostol had a longer mean induction to birth interval when compared with those women administered prostaglandin F_{2alpha} (MD 9.40, 95% CI 4.9 to 13.90 (one study, 133 women)). There were no statistically significant differences identified for the following outcomes: need for surgical evacuation of the uterus; nausea; vomiting; diarrhoea; and pyrexia.

Combined oral and loading dose vaginal misoprostol versus vaginal misoprostol alone (Analysis 11)

We included two studies involving 98 women. Women who received vaginal misoprostol alone had a longer mean induction to birth interval (MD 5.20, 95% CI 3.42 to 6.98 (one study, 43 women)) when compared with women who were administered oral misoprostol following a loading dose of vaginal misoprostol. There were no statistically significant differences identified for the following outcomes: vaginal birth not achieved in 24 hours; need for analgesia; surgical evacuation of the uterus; and side effects (nausea, vomiting, and diarrhoea).

Combined oral and loading dose vaginal misoprostol versus oral misoprostol alone (Analysis 12)

We identified one study involving 56 women. The addition of a loading dose of vaginal misoprostol reduced the chance of a woman not achieving vaginal birth within 24 hours when compared with oral misoprostol alone (RR 0.47, 95% CI 0.23 to 0.96 (one study, 56 women)). There were no other differences identified between the two methods of induction for the following outcomes: need for analgesia; surgical evacuation of the uterus; or side effects (nausea, vomiting, or diarrhoea).

Combined oral and loading dose vaginal misoprostol versus dilation and evacuation (Analysis 13)

We identified one study involving 18 women. There were no statistically significant differences identified between the two methods for the outcomes nausea, vomiting, or diarrhoea.

Sublingual misoprostol versus vaginal misoprostol (Analysis 14)

We identified two studies involving 202 women. Women who were administered sublingual misoprostol were more likely to achieve vaginal birth within 24 hours (RR 0.24, 95% CI 0.08 to 0.74 (two studies, 202 women)) and had a shorter mean induction to birth interval (MD -4.81 hours, 95% CI -8.26 to -1.37; I^2 = 66%, random-effects (two studies, 202 women)) when compared with administration of vaginal misoprostol. There were no other differences identified between the two methods of induction for the following outcomes: need for analgesia; side effects (vomiting, diarrhoea, or pyrexia).

Sublingual misoprostol versus oral misoprostol (Analysis 15)

We identified two studies involving 204 women. Women who were administered sublingual misoprostol had a shorter mean induction to birth interval (MD -7.17 hours, 95% CI -13.73 to -0.60; I^2 = 88%, random-effects (two studies, 202 women)) but were no more likely to achieve vaginal birth within 24 hours (RR 0.22, 95% CI 0.01 to 4.99; I^2 = 75%, random-effects (two studies, 204 women)) when compared with administration of oral misoprostol. There were no other differences identified between the two methods of induction for the following outcomes: need for analgesia; and side effects (vomiting, diarrhoea, or pyrexia).

Sublingual misoprostol 100 mcg versus sublingual misoprostol 200 mcg (Analysis 16)

We identified one study involving 81 women. There were no statistically significant differences identified between the two doses of misoprostol for the following outcomes: vomiting, diarrhoea, or pyrexia.

Low dose vaginal misoprostol (< 800 mcg) versus moderate dose vaginal misoprostol (800 mcg to 2400 mcg) (Analysis 17)

We identified a single study involving 150 women. The use of lower cumulative doses of misoprostol was associated with an increased chance of a woman not achieving vaginal birth within 24 hours when compared with moderate doses of misoprostol (RR 1.85, 95% CI 1.13 to 3.03 (one study, 150 women)), and a reduction in the need for surgical evacuation of the uterus (RR 0.57, 95% CI 0.33 to 0.98 (one study, 150 women)). There were no significant differences identified for the following outcomes: need for analgesia; or side effects (nausea, vomiting, or diarrhoea).

Moderate dose vaginal misoprostol (800 mcg to 2400 mcg) versus high dose vaginal misoprostol (greater than 2400 mcg) (Analysis 18)

We identified a single study involving 178 women. The use of moderate cumulative doses of misoprostol over a 24-hour period was associated with an increased mean induction to birth interval when compared with higher doses of misoprostol (MD 4.20 hours, 95% CI 1.36 to 7.04 (one study, 178 women)).

Subgroup analyses

It was not possible to explore the effect of induction of labour in the presence of a live fetus or following intrauterine fetal death. Where studies included both indications for termination of pregnancy, outcomes were not reported separately by indication for induction, or by the method of induction used. It was not possible to explore the effect of gestational age on the termination process, as studies did not separately report outcomes for women undergoing termination in the second or third trimester of pregnancy. Similarly, it was not possible to explore the effect of maternal parity, or the presence of a prior caesarean birth on the induction process, as women with a scarred uterus were often excluded from the trials.

DISCUSSION

Misoprostol is being used widely in the obstetric community as an agent to induce labour for termination of pregnancy in the second and third trimesters of pregnancy for fetal anomaly or following intrauterine fetal demise. This systematic review includes the available randomised controlled trials comparing the use of misoprostol in second and third trimester of pregnancy with other methods of labour induction to terminate pregnancy. Overall, the quality of the trials available for inclusion was reasonable, although there was considerable variation in the outcomes reported, and in the regimen of misoprostol adopted.

When compared with agents that have traditionally been used to induce labour in this setting (for example, gemeprost, prostaglandin E_2 and prostaglandin F_{2alpha}), vaginal misoprostol is as effective in effecting vaginal birth within 24 hours, with a similar induction to birth interval. When compared with other prostaglandin preparations, the occurrence of maternal gastrointestinal side effects such as nausea, vomiting, and diarrhoea is reduced with the use of vaginal misoprostol. While the different treatments involving various prostaglandin preparations appear comparable for the reported outcomes, the information available regarding rare maternal complications, such as uterine rupture, is limited.

The use of oral misoprostol for induction of labour for termination in the second and third trimesters of pregnancy for fetal anomaly or following intra-uterine fetal demise, is less effective than vaginal misoprostol, with women experiencing a longer induction to birth interval, and an increased chance of remaining undelivered 24 hours after the induction process commences. The more limited information available about the use of sublingual misoprostol in this setting would suggest that it is more effective than both oral or vaginal administration. Information about women's preferences for an oral induction method in this clinical setting is limited, with suggestions that satisfaction with the induction process is more related to the duration of the induction rather than the route of administration of medication (Akoury 2004; Dickinson 2003; Grimes 2005).

The Cochrane systematic reviews of the use of oral (Hofmeyr 2003) and vaginal (Alfirevic 2006) misoprostol for induction of labour at term in the presence of a live fetus identified significant variation in both the dose and frequency of drug administration, concluding that at present, the optimal regimen for misoprostol is uncertain. Similarly, there is wide variation in the dose, frequency of administration and route of administration of misoprostol to effect termination of pregnancy in the second or third trimester of pregnancy. There have been calls for further investigation of the lowest effective dose of misoprostol to induce labour at term in the presence of a live fetus, to ensure minimal side effects for the woman, and maintain safety for both the woman and fetus (Alfirevic 2006; Hofmeyr 2003). These efforts have been somewhat hampered by the preparation of misoprostol as a 100 mcg or 200 mcg tablet. Concerns about fetal safety and avoidance of toxicity are not relevant in the situation of induction of labour following fetal death or to effect termination of pregnancy in the second and third trimester. However, issues of side effects and safety for the woman remain. While this meta-analysis indicates a low occurrence of medication side effects with the use of misoprostol, not all trials provided this information. There are insufficient data to assess the occurrence of rare but potentially life threatening complications for the woman, including uterine rupture, with not all trials reporting serious adverse outcomes, and at present a combined sample size underpowered to be able to detect all but large differences.

The use of low doses of misoprostol must take into account the re-

ceptivity of the uterus to prostaglandin agents, particularly at early gestational ages. The use of lower doses of misoprostol was associated with an increased chance of a woman not achieving vaginal birth within 24 hours, and a longer induction to birth interval, when compared with higher doses of misoprostol. In this situation, low dose medication may be ineffective in inducing labour or result in an unacceptably long induction to delivery interval. However, the increased dose of misoprostol to effect termination must be balanced against an increase in the occurrence of maternal gastrointestinal side effects. The effect of increasing the dose of misoprostol on the occurrence of rare but potentially life threatening maternal complications remains uncertain.

Future research efforts should be directed towards determining the optimal dose and frequency of administration, with particular attention to standardised reporting of all relevant outcomes and assessment of rare adverse events. Further information is required about the use of sublingual misoprostol in this clinical setting.

AUTHORS' CONCLUSIONS

Implications for practice

The use of vaginal misoprostol in the termination of second and third trimester of pregnancy is as effective as other prostaglandin preparations (including cervagem, prostaglandin E_2 and prostaglandin F_{2alpha}), and more effective than oral administration of misoprostol. However, important information regarding maternal safety, and in particular the occurrence of rare outcomes such as uterine rupture, remains limited.

Implications for research

Future research efforts should be directed towards determining the optimal dose and frequency of administration, with particular attention to standardised reporting of all relevant outcomes and assessment of rare adverse events. Further information is required about the use of sublingual misoprostol in this clinical setting.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Akoury 2004

Methods	Trial conducted in Canada, January 1998-February 2001.
Participants	240 women with singleton pregnancy undergoing termination of pregnancy for fetal anomaly at 15 to 24 weeks' gestation. Women were excluded if hypersensitivity to prostaglandins, prior classical caesarean section, hysterotomy, active bleeding, severe asthma, severe oligohydramnios, or prelabour ruptured membranes.
Interventions	Women randomised to 1) intra-amniotic prostaglandin F2alpha and laminaria; 2) oral misoprostol (400 mcg at 4-hourly intervals); or 3) vaginal misoprostol (400 mcg at 4-hourly intervals).
Outcomes	Mean induction to delivery interval; surgical evacuation of the uterus; nausea; vomiting; diarrhoea; pyrexia.
Notes	Method of randomisation: computer generated. Allocation concealment: opaque sealed envelopes. Blinding of participants, caregivers and outcome assessors: no.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated.
Allocation concealment?	Yes	Sealed opaque envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Bebbington 2002

Methods	Trial conducted in Canada, September 1998-November 2001.
Participants	114 women undergoing second trimester termination of pregnancy following both fetal demise or termination of a live fetus. Women were excluded if hypersensitive to prostaglandins or had limited English.

Bebbington 2002 (*Continued*)

Interventions	Women randomised to vaginal misoprostol (400 mcg at 4-hourly intervals) or oral misoprostol (200 mcg at hourly intervals for 3 hours then 400 mcg at 4-hourly intervals) .
Outcomes	Vaginal birth not achieved within 24 hours; induction to birth interval; mean blood loss; surgical evacuation of the uterus; serious maternal morbidity; pyrexia.
Notes	Method of randomisation: random number table. Allocation concealment: opaque sealed envelopes. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Yes	Opaque sealed envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Behrashi 2008

Methods	Trial conducted in Iran, 2006.
Participants	60 women with second trimester genetic termination of pregnancy or intrauterine fetal death. Exclusion if placenta praevia, contraindication to prostaglandin therapy, convulsions, glaucoma or inflammatory bowel disease.
Interventions	Vaginal misoprostol 400 mcg (to maximum 4 doses) vs oral misoprostol 400 mcg (to maximum 4 doses).
Outcomes	Induction to delivery interval; surgical evacuation of uterus.
Notes	Method of randomisation: stated to be "randomized trial". Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessor: not stated.

Behrashi 2008 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Stated to be "randomized trial".
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Not stated.
Free of other bias?	Yes	

Caliskan 2005

Methods	Trial conducted in Turkey, January-December 2003.
Participants	153 women at 13 to 20 weeks' gestation presenting for termination with either fetal anomaly or intrauterine fetal death. Women with an allergy to misoprostol were excluded from the study.
Interventions	Women randomised to 1) oral misoprostol (100 mcg at 2 hourly intervals); 2) vaginal misoprostol (200 mcg at 4 hourly intervals); or 3) sublingual misoprostol (100 mcg at 2 hourly intervals).
Outcomes	Vaginal birth not achieved in 24 hours; induction to delivery interval; analgesic requirements; side effects.
Notes	Method of randomisation: computer generated sequence. Allocation concealment: unclear (possibly sealed opaque envelopes). Blinding: participants, caregivers and outcome assessor - no.

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated sequence.
Allocation concealment?	Unclear	Unclear - possible use of sealed opaque envelopes.

Caliskan 2005 (*Continued*)

Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Unclear	Unable to assess.

Caliskan 2009

Methods	Trial conducted in Turkey, January 2004-January 2007.
Participants	162 women presenting in the second trimester of pregnancy with either fetal anomaly or intrauterine fetal death requiring termination of pregnancy. Women with an allergy to prostaglandins or asthma were excluded from participation.
Interventions	Women were randomised to 1) sublingual misoprostol (100 mcg 2 hourly intervals); or 2) sublingual misoprostol (200 mcg 2 hourly intervals).
Outcomes	Induction to delivery interval; maternal side effects.
Notes	Method of randomisation: computer-generated sequence. Allocation concealment: sealed opaque envelopes. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated sequence.
Allocation concealment?	Yes	Sealed opaque envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Chittacharoen 2003

Methods	Trial conducted in Thailand, July 1999-June 2001.
Participants	80 women undergoing second or third trimester (16 to 41 weeks' gestation) termination of pregnancy following both fetal demise or termination of a live fetus. Women were excluded if prior classical caesarean section or hypersensitive to prostaglandins.
Interventions	Women randomised to vaginal misoprostol (200 mcg at 12-hourly intervals) or oral misoprostol (400 mcg at 4-hourly intervals).
Outcomes	Vaginal birth not achieved within 24 hours; induction to birth interval; narcotic analgesia requirements; nausea; vomiting; diarrhoea; pyrexia.
Notes	Method of randomisation: random number table. Allocation concealment: opaque sealed envelopes. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Yes	Opaque sealed envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Dickinson 1998

Methods	Trial conducted in Australia, July 1996-February 1997.
Participants	150 women undergoing second trimester termination of pregnancy fetal anomalies or following intrauterine fetal death; trial stopped early after total 100 women randomised.
Interventions	Women randomised to 1) vaginal misoprostol (200 mcg at 6-hourly intervals); 2) vaginal gemeprost (1 mg at 3-hourly intervals).
Outcomes	Vaginal birth not achieved in 24 hours; median induction to birth interval; pain score > 5 (using VAS); analgesia requirements; surgical evacuation of the uterus; nausea; vomiting; diarrhoea; pyrexia.

Dickinson 1998 (*Continued*)

Notes	Method of randomisation: random number table. Allocation concealment: opaque sealed envelopes. Blinding of participants (yes), caregivers (no) and outcome assessors (yes).

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Yes	Opaque sealed envelopes.
Blinding? All outcomes	Yes	Blinding of participants and outcome assessor.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Unclear	Trial stopped early.

Dickinson 2002

Methods	Trial conducted in Australia, March 1998-February 1999.
Participants	150 women undergoing second or third trimester termination of pregnancy for fetal anomaly or after intrauterine fetal death.
Interventions	Women randomised to 1) vaginal misoprostol (200 mcg at 6-hourly intervals); 2) vaginal misoprostol (400 mcg at 6-hourly intervals); or 3) vaginal misoprostol loading dose (600 mcg) followed by vaginal misoprostol (200 mcg at 6-hourly intervals).
Outcomes	Vaginal birth not achieved in 24 hours; median induction to birth interval; pain score > 5 (using VAS); analgesia requirements; surgical evacuation of the uterus; nausea; vomiting; diarrhoea.
Notes	Method of randomisation: random number table. Allocation concealment: opaque sealed envelopes. Blinding of participants, caregivers and outcome assessors: no.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table.

Dickinson 2002 (*Continued*)

Allocation concealment?	Yes	Opaque sealed envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Dickinson 2003

Methods	Trial conducted in Australia, March 2001-July 2002.
Participants	225 women undergoing second trimester termination of pregnancy for termination of a live fetus with anomalies; trial stopped early after total 84 women randomised.
Interventions	Women randomised to 1) vaginal misoprostol (400 mcg at 6-hourly intervals); 2) oral misoprostol (200 mcg at 3-hourly intervals); or 3) vaginal misoprostol loading dose (600 mcg) followed by oral misoprostol (200 mcg at 3-hourly intervals).
Outcomes	Vaginal birth not achieved in 24 hours; induction to delivery interval (median); median pain score; need for analgesia; surgical evacuation; nausea; vomiting; diarrhoea; median maternal satisfaction.
Notes	Method of randomisation: random number table. Allocation concealment: opaque sealed envelopes. Blinding of participants, caregivers and outcome assessors: no.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Yes	Sealed opaque envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Dickinson 2003 (*Continued*)

Free of other bias?	Yes	

Elhassan 2008

Methods	Trial conducted in Sudan, February-November 2006.
Participants	150 women with intrauterine fetal death in the second trimester of pregnancy. Women with prior uterine surgery, asthma, heart disease or more than 7 previous pregnancies were excluded from the study.
Interventions	Women were randomised to 1) oral misoprostol (100 mcg at 4-hourly intervals); 2) vaginal misoprostol (100 mcg at 4-hourly intervals); or 3) sublingual misoprostol (100 mcg at 4-hourly intervals).
Outcomes	Vaginal birth not achieved in 24 hours; induction to delivery interval.
Notes	Method of randomisation: stated to be an "open randomised controlled clinical trial". Allocation concealment: not stated. Blinding of participants, caregivers, outcome assessors: no.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Stated to be an "open randomised controlled clinical trial".
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Fadalla 2004

Methods	Trial conducted in Sudan, February-December 2002.
Participants	70 women undergoing second trimester termination of pregnancy following fetal demise. Women were excluded with prior uterine surgery, severe asthma, heart disease, parity greater than 7.

Fadalla 2004 (*Continued*)

Interventions	Women randomised to vaginal misoprostol (100 mcg at 4-hourly intervals) or oral misoprostol (100 mcg at 4-hourly intervals).
Outcomes	Mean induction to birth interval; surgical evacuation of the uterus.
Notes	Method of randomisation: 'patients were randomised'. Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessors: no.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Stated that "patients were randomised".
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Feldman 2003

Methods	Trial conducted in United States, January 2000-June 2002.
Participants	40 women undergoing second trimester termination of pregnancy following fetal demise. Women were excluded with hypersensitivity to prostaglandins, scarred uterus.
Interventions	Women received vaginal misoprostol (800 mcg) and were then randomised to followed by either vaginal misoprostol (400 mcg at 8-hourly intervals) or oral misoprostol (400 mcg at 8-hourly intervals).
Outcomes	Mean induction to birth interval; analgesic requirements (% only), surgical evacuation of the uterus, side effects (% only).
Notes	Method of randomisation: random number table. Allocation concealment: opaque sealed envelopes. Blinding of participants, caregivers and outcome assessors: no.

Risk of bias

Feldman 2003 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Yes	Opaque sealed envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Ghorab 1998

Methods	Trial conducted in Egypt; gestational age 16 to 24 weeks.
Participants	40 women undergoing termination of pregnancy following both fetal demise or termination of a live fetus.
Interventions	Women randomised to vaginal misoprostol (200 mcg at 8 hourly intervals) or intracervical prostaglandin F2 alpha.
Outcomes	Vaginal birth not achieved within 24 hours; induction to birth interval; surgical evacuation of the uterus; vomiting; diarrhoea; pyrexia.
Notes	Method of randomisation: "randomly allocated". Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Stated that patients were "randomly allocated".
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	

Free of selective reporting?	Yes	
Free of other bias?	Yes	

Gilbert 2001

Methods	Trial conducted in New Zealand, July 1997-June 1998; trial stopped early.
Participants	55 women undergoing second trimester termination of a live fetus.
Interventions	Women randomised to vaginal misoprostol (400 mcg followed by 200 mcg 2 hours later, followed by 200 mcg at 4-hourly intervals) or oral misoprostol (400 mcg followed by 200 mcg 2 hours later, followed by 200 mcg at 4-hourly intervals).
Outcomes	Vaginal birth not achieved within 24 hours; induction to birth interval; surgical evacuation of the uterus.
Notes	Method of randomisation: random number table generated by coin toss. Allocation concealment: not stated. Blinding of participants, caregivers or outcome assessors: no.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table generated by coin toss.
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Unclear	Trial stopped early.

Grimes 2005

Methods	Trial conducted in United States, January 2002-January 2003.
Participants	60 women undergoing second trimester termination for fetal anomalies or following intrauterine fetal death; trial stopped after 18 women recruited due to poor recruitment rates. Women were excluded if prior caesarean section, myomectomy, renal failure, severe

	asthma.
Interventions	Women randomised to mifepristone followed by vaginal misoprostol (800 mcg) followed by oral misoprostol (400 mcg 3-hourly intervals) or surgical dilation and evacuation.
Outcomes	Nausea; vomiting; diarrhoea; median maternal satisfaction.
Notes	Method of randomisation: computer-generated random number table. Allocation concealment: sealed opaque envelopes. Blinding of participants, caregivers or outcome assessors: no.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated random number table.
Allocation concealment?	Yes	Sealed opaque envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Herabutya 1997

Methods	Trial conducted in Thailand, January 1995-February 1997.
Participants	54 women with an intrauterine fetal death between 14 and 39 weeks' gestation were included.
Interventions	Women were randomised to 1) vaginal misoprostol (100 mcg) or 2) Intracervical prostaglandin E2 gel (3 mg).
Outcomes	Vaginal birth not achieved in 24 hours; induction to delivery interval; analgesic requirements; surgical evacuation of the uterus; maternal side effects.
Notes	Method of randomisation: stated that "patients were randomised". Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Herabutya 1997 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Stated that "patients were randomised".
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Herabutya 2005

Methods	Trial conducted in Thailand, December 2000-December 2003.
Participants	276 women undergoing second trimester termination for fetal anomalies or following intrauterine fetal death. Women were excluded with cardiac disease, severe asthma, hepatic or renal disease, or prelabour ruptured membranes.
Interventions	Women randomised to vaginal misoprostol (600 mcg at 6-hourly intervals) or vaginal misoprostol (600 mcg at 12-hourly intervals).
Outcomes	Vaginal birth not achieved within 24 hours; induction to birth interval (median); analgesia requirements; blood loss greater than 500 mL; need for blood transfusion; surgical evacuation of the uterus; nausea; vomiting; diarrhoea; fever.
Notes	Method of randomisation: random number table. Allocation concealment: sealed opaque envelopes. Blinding of participants, caregivers or outcome assessors: no.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Yes	Sealed opaque envelopes.
Blinding? All outcomes	Unclear	Not stated.

Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Hidar 2001

Methods	Trial conducted in France, December 1999-September 2000.
Participants	90 women undergoing termination of pregnancy following both fetal demise or termination of a live fetus. Women excluded if scarred uterus, vaginal bleeding, cervical dilation more than 2 cm on admission.
Interventions	Women randomised to vaginal misoprostol (200 mcg at 12-hourly intervals) or vaginal misoprostol (200 mcg at 12-hourly intervals) with oxytocin.
Outcomes	Vaginal birth not achieved in 24 hours (% only); mean induction to birth interval; surgical evacuation of uterus; vomiting; diarrhoea; pyrexia.
Notes	Method of randomisation: random number table. Allocation concealment: not stated. Blinding of participants, caregivers or outcome assessors: no.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Hidar 2005

Methods	Trial conducted in Tunisia, January 2003-July 2004.
Participants	36 women undergoing termination of pregnancy following both fetal demise or termination of a live fetus. Women excluded if hypersensitive to prostaglandins, more than 1 prior caesarean section, severe asthma, glaucoma, vaginal bleeding, anaemia, blood pressure less than 120/80.
Interventions	Women randomised to vaginal misoprostol (200 mcg at 12-hourly intervals) or vaginal misoprostol (200 mcg at 12-hourly intervals) with vaginal nitric oxide donor.
Outcomes	Vaginal birth not achieved in 24 hours; mean induction to delivery interval; side effects (any).
Notes	Method of randomisation: stated to be 'random'. Allocation concealment: sealed opaque envelopes. Blinding of participants, caregivers or outcome assessors: no.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Stated to be "random".
Allocation concealment?	Yes	Sealed opaque envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Jain 1994

Methods	Trial conducted in United States of America; gestational age 12 to 22 weeks.
Participants	55 women undergoing termination of pregnancy following both fetal demise or termination of a live fetus
Interventions	Women randomised to vaginal misoprostol (200 mcg at 12-hourly intervals) or vaginal prostaglandin E2 (20 mg at 3-hourly intervals).
Outcomes	Vaginal birth not achieved within 24 hours; induction to birth interval; narcotic analgesia requirements; blood loss; need for blood transfusion; surgical evacuation of the uterus; vomiting; diarrhoea; pyrexia.

Jain 1994 (*Continued*)

Notes	Method of randomisation: random number table. Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Jain 1996

Methods	Trial conducted in United States of America; gestational age 12 to 22 weeks.
Participants	68 women undergoing termination of pregnancy following both fetal demise or termination of a live fetus. Women excluded if uterine incision, cervical dilatation, maternal infection, maternal pulmonary, renal, hepatic or cardiovascular disease.
Interventions	Women randomised to vaginal misoprostol (200 mcg at 12-hourly intervals) or vaginal misoprostol (200 mcg at 12-hourly intervals) and laminarae.
Outcomes	Vaginal birth not achieved within 24 hours; blood loss; need for blood transfusion; vomiting; diarrhoea; pyrexia.
Notes	Method of randomisation: women were "randomised". Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Stated that "women were randomised".
Allocation concealment?	Unclear	Not stated.

Jain 1996 (*Continued*)

Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Jain 1999

Methods	Trial conducted in United States of America; gestational age 12 to 22 weeks.
Participants	100 women undergoing termination of pregnancy following both fetal demise or termination of a live fetus. Women excluded if prior uterine incision, maternal infection, cervical dilatation, uterine bleeding, or maternal pulmonary, hepatic, renal or cardiovascular disease.
Interventions	Women randomised to vaginal misoprostol (200 mcg at 6-hourly intervals) or vaginal misoprostol (200 mcg at 12-hourly intervals).
Outcomes	Vaginal birth not achieved within 24 hours; induction to birth interval; narcotic analgesia requirements; need for blood transfusion; surgical evacuation of the uterus; vomiting; diarrhoea; pyrexia.
Notes	Method of randomisation: random number table. Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Jansen 2008

Methods	Trial conducted in the Netherlands, May 2003-August 2004.
Participants	16 women with single fetus in second trimester of pregnancy (14 to 24 weeks' gestation) where termination for fetal anomalies. Women with uterine scar or contraindication to the use of misoprostol or mifepristone were excluded.
Interventions	Women were randomised to 1) mifepristone followed by vaginal misoprostol (200 mcg at 3-hourly intervals) or 2) vaginal hydrophilic rods (Dilapan) and infusion of prostaglandin E2 (sulprostone).
Outcomes	Vaginal birth not achieved in 24 hours; induction to delivery interval.
Notes	Method of randomisation: random number table. Allocation concealment: opaque sealed envelopes. Blinding of participants, caregivers, outcome assessors: not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Yes	Opaque sealed envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Kara 1999

Methods	Trial conducted in Turkey.
Participants	65 women with a second trimester intrauterine fetal death. Women excluded with asthma, cardiac disease, bleeding or coagulation problem.
Interventions	Women were randomised to 1) vaginal misoprostol (200 mcg) or 2) vaginal dinoprostone (0.5 mg).
Outcomes	Induction to delivery interval; blood loss; surgical evacuation of uterus; maternal side effects.

Kara 1999 (*Continued*)

Notes	Method of randomisation: stated that "randomly allocated to two groups". Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Stated that "randomly allocated to two groups".
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Makhlouf 2003

Methods	Trial conducted in Egypt, May 2000-May 2001.
Participants	130 women undergoing termination of pregnancy following both fetal demise or termination of a live fetus for anomalies. Women excluded if hypersensitivity to prostaglandins, scarred uterus, transverse lie, placenta praevia, parity greater than 5 or prelabour ruptured membranes.
Interventions	Women randomised to vaginal misoprostol (100 mcg at 4-hourly intervals) or vaginal PGE2 at 6-hourly intervals; or vaginal GTN (500 mcg at 6-hourly intervals).
Outcomes	Vaginal birth not achieved within 24 hours (% only); mean induction to birth interval; analgesia requirements; surgical evacuation of uterus; side effects (any); vomiting; diarrhoea; pyrexia.
Notes	Method of randomisation: random number table. Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table.

Makhlouf 2003 (*Continued*)

Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Munthali 2001

Methods	Trial conducted in South Africa; gestational age 18 to 26 weeks.
Participants	61 women undergoing termination of pregnancy for "obstetric indications" with both live fetus and following fetal death. Women excluded if prior caesarean section, scarred uterus, grand multiparous woman, multiple pregnancy, ruptured membranes, antepartum haemorrhage, overt vaginal infection, prostaglandin allergy.
Interventions	Women randomised to vaginal misoprostol (400 mcg at 6-hourly intervals) or extra-amniotic prostaglandin F2 alpha.
Outcomes	Induction to birth interval; significant haemorrhage; surgical evacuation of the uterus; any side effect.
Notes	Method of randomisation: computer-generated random number table. Allocation concealment: opaque sealed envelope. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated random number table.
Allocation concealment?	Yes	Opaque sealed envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Free of other bias?	Yes	

Nakintu 2001

Methods	Trial conducted in Uganda.
Participants	120 women undergoing termination of pregnancy for fetal anomalies or following intrauterine fetal death. Women excluded if any contraindication to induction of labour.
Interventions	Women randomised to vaginal misoprostol (50 mcg doubled every 6 hours) intervals) or oxytocin.
Outcomes	Vaginal birth not achieved in 24 hours (% only); induction to birth interval (mean; no standard deviation); analgesia requirements (% only); surgical evacuation of uterus (% only).
Notes	Method of randomisation: computer-generated random number table. Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated random number table.
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Neto 1988

Methods	Trial conduced Sao Paulo, Brazil, March-June 1988.
Participants	15 women with intrauterine fetal death.
Interventions	Women were randomised to 1) oral misoprostol (400 mcg at 4-hourly intervals); 2) oral misoprostol (200 mcg at 4-hourly intervals); or 3) vaginal misoprostol (200 mcg single dose).

Neto 1988 (*Continued*)

Outcomes	Onset to time of first contraction; time to attain peak uterine activity; no other outcomes reported.
Notes	Method of randomisation: stated to be "randomly allocated". Allocation concealment: not stated. Blinding of participants, caregivers or outcome assessors: not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Stated to be "randomly allocated".
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Niromanesh 2005

Methods	Trial conducted in Iran.
Participants	100 women undergoing second trimester termination of pregnancy following intrauterine fetal death.
Interventions	Women randomised to vaginal misoprostol (400 mcg at 12-hourly intervals) or vaginal misoprostol (600 mcg at 12-hourly intervals).
Outcomes	Outcomes presented only as %; no denominators presented.
Notes	Method of randomisation: "patients were randomised". Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Stated that "patients were randomised".
Allocation concealment?	Unclear	Not stated.

Niromanesh 2005 (*Continued*)

Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Unclear	Unable to assess.
Free of selective reporting?	Unclear	Unable to assess.
Free of other bias?	Unclear	Unable to assess.

Nor Azlin 2006

Methods	Trial conducted in Malaysia.
Participants	54 women at 14 to 26 weeks' gestation, with either intrauterine fetal death or fetal anomaly undergoing termination of pregnancy were involved. Women were excluded if a multiple pregnancy, or if there was a contraindication or allergy to the medication.
Interventions	Women were randomised to 1) vaginal misoprostol (200 mcg at 12-hourly intervals) or 2) vaginal gemeprost (cervagem) (1 mg at 3-hourly intervals).
Outcomes	Vaginal birth not achieved in 24 hours; induction to delivery interval; analgesic requirements; surgical evacuation of uterus; maternal side effects.
Notes	Method of randomisation: stated that trial was "randomised". Allocation concealment: sealed opaque envelopes. Blinding of participants, caregivers, and outcome assessors: not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Stated that trial was "randomised".
Allocation concealment?	Yes	Sealed opaque envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Nuutila 1997

Methods	Trial conducted in Finland, June 1995-May 1996.
Participants	81 women undergoing second trimester termination of pregnancy for fetal anomalies or following intrauterine fetal death. Women excluded if uterine scar; contractions; bleeding vaginally.
Interventions	Women randomised to vaginal misoprostol (100 mcg at 6-hourly intervals) or vaginal misoprostol (200 mcg at 12-hourly intervals), or gemeprost (1 mg at 3-hourly intervals) .
Outcomes	Mean induction to birth interval; analgesia requirements; surgical evacuation of the uterus; vomiting; diarrhoea.
Notes	Method of randomisation: random number table. Allocation concealment: sealed opaque envelopes. Blinding of participants, caregivers and outcome assessors: no.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Yes	Sealed opaque envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Nyende 2004

Methods	Trial conducted in South Africa.
Participants	38 women in second or third trimester of pregnancy with intrauterine fetal death. Women were excluded with fetal malpresentation, macrosomia, uterine scar, contraindication to prostaglandin medication, hepatic failure or renal failure.
Interventions	Women were randomised to 1) oral misoprostol (200 mcg at 6-hourly intervals) or 2) vaginal misoprostol (200 mcg at 6-hourly intervals).
Outcomes	Induction to delivery interval; serious maternal morbidity; maternal side effects.

Notes	Method of randomisation: "Envelope picked at random". Allocation concealment: sealed envelopes. Blinding of participants, caregivers, and outcome assessors: not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Envelope picked at random".
Allocation concealment?	Unclear	Sealed envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Owen 1999

Methods	Trial conducted in United States of America.
Participants	30 women undergoing termination of pregnancy following both fetal demise or termination of a live fetus (gestational age 16 to 24 weeks). Women excluded if severe pre-eclampsia, cervical dilatation greater than 2 cm or sensitivity to prostaglandins.
Interventions	Women randomised to vaginal misoprostol (200 mcg at 12-hourly intervals) or vaginal prostaglandin E2 (40 mg) and concentrated oxytocin infusion.
Outcomes	Vaginal birth not achieved within 24 hours; induction to birth interval; surgical evacuation of the uterus.
Notes	Method of randomisation: computer-generated random number table. Allocation concealment: opaque sealed envelopes. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random number table.

Owen 1999 (*Continued*)

Allocation concealment?	Yes	Opaque sealed envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Perry 1999

Methods	Trial conducted United States of America.
Participants	51 women undergoing termination of pregnancy with a live fetus with fetal anomaly (gestational age 17 to 24 weeks). Women excluded if fetal death, oligohydramnios, or contraindication to the use of prostaglandins.
Interventions	Women randomised to vaginal misoprostol (200 mcg at 12-hourly intervals) with laminarae or intra-amniotic prostaglandin F2 alpha and laminarae.
Outcomes	Vaginal birth not achieved within 24 hours; induction to birth interval; mean blood loss; surgical evacuation of the uterus; nausea; vomiting; diarrhoea; pyrexia.
Notes	Method of randomisation: computer-generated random number table. Allocation concealment: opaque sealed envelopes. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated random number table.
Allocation concealment?	Yes	Sealed opaque envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Perry 1999 (*Continued*)

Free of other bias?	Yes	

Pongsatha 2004

Methods	Trial conducted in Thailand.
Participants	178 women undergoing second trimester termination of pregnancy for fetal anomalies or following intrauterine fetal death. Women excluded if labour, hypersensitive to prostaglandins, prior classical caesarean section.
Interventions	Women randomised to vaginal misoprostol (400 mcg at 3-hourly intervals) or vaginal misoprostol (400 mcg at 6-hourly intervals).
Outcomes	Vaginal birth not achieved within 24 hours (% only); mean induction to birth interval.
Notes	Method of randomisation: "patients were randomised". Allocation concealment: not stated. Blinding of participants, caregivers and outcome assessors: not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Stated that "patients were randomised".
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Ramsey 2004

Methods	Trial conducted in United States, April 1999-May 2002.
Participants	100 women undergoing second trimester termination of pregnancy for fetal anomalies or following intrauterine fetal death. Women excluded if hypersensitivity to prostaglandins, clinical chorioamnionitis, prior caesarean section or uterine surgery, active labour, placenta praevia.

Ramsey 2004 (*Continued*)

Interventions	Women randomised to vaginal misoprostol (600 mcg followed by 400 mcg at 4-hourly intervals) or vaginal PGE2 and oxytocin.
Outcomes	Vaginal birth not achieved within 24 hours; mean induction to delivery interval; analgesia requirements; blood loss greater than 500 mL; surgical evacuation of the uterus; nausea or vomiting; diarrhoea; pyrexia.
Notes	Method of randomisation: computer-generated random number table. Allocation concealment: opaque sealed envelopes. Blinding of participants, caregivers and outcome assessors: no.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random number table.
Allocation concealment?	Yes	Opaque sealed envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Su 2005

Methods	Trial conducted in Singapore, October 2002-April 2004.
Participants	132 women undergoing second trimester termination of pregnancy for fetal anomalies or following intrauterine fetal death. Women excluded if hypersensitive to prostaglandins, 2 or more prior caesarean sections, multiple pregnancy, severe asthma, oligohydramnios.
Interventions	Women randomised to vaginal misoprostol (400 mcg at 3-hourly intervals) or intra-amniotic prostaglandin F2alpha.
Outcomes	Vaginal birth not achieved within 24 hours; mean induction to birth interval; surgical evacuation of the uterus; nausea; vomiting; diarrhoea; pyrexia.
Notes	Method of randomisation: computer generated random number table. Allocation concealment: opaque sealed envelopes. Blinding of participants, caregivers and outcome assessors: no.

Su 2005 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated random number table.
Allocation concealment?	Yes	Sealed opaque envelopes.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Zuo 1998

Methods	Trial conducted in China.
Participants	80 women undergoing termination of pregnancy between 13 and 26 weeks' gestation with fetal anomaly. Women excluded if hypersensitive to prostaglandins.
Interventions	Women randomised to 1) vaginal misoprostol (200 mcg at 24-hourly intervals) or 2) Carboprost (1 mg at 3-hourly intervals).
Outcomes	Induction to delivery interval; analgesic requirements; maternal side effects.
Notes	Method of randomisation: computer-generated. Allocation concealment: not stated. Blinding of participants, caregivers, outcome assessors: not stated.

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated random number sequence.
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Unclear	Unable to assess.

Zuo 1998 (*Continued*)

Free of selective reporting?	Unclear	Unable to assess.
Free of other bias?	Unclear	Unable to assess.

GTN:glyceryl trinitrate
mcg: micrograms
mg: milligrams
mL: millilitres
PGE2: prostaglandin E2
VAS: visual analogue scale
vs: versus

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

Ayudhaya 2006	Included women 7 to 12 weeks' gestation with early pregnancy failure.
Biswas 2007	Recruited women requesting abortion; no indication that involved women with fetal death or termination for fetal anomalies.
El-Refaey 1995	Recruited women requesting social termination of pregnancy.
Eng 1997	Quasi-randomisation using odd/even number allocation.
Gonzalez 2001	All women received misoprostol to effect termination of pregnancy. Randomisation was to administration of medication in an inpatient or outpatient setting.
Guix 2005	Randomised women undergoing termination of pregnancy for 'social' indications.
Herabutya 2001	Quasi-randomisation using odd/even number allocation.
Marquette 2005	57% of women recruited to the study were requesting termination for unplanned pregnancy or social indications.
Nigam 2006	Recruited women requesting abortion; no indication that involved women with fetal death or termination for fetal anomalies.
Saha 2006	Recruited women requesting abortion; no indication that involved women with fetal death or termination for fetal anomalies.
Yapar 1996	Quasi-randomisation methods; more than 15% post-randomisation exclusions.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Abdel Fattah 1997

Methods	Stated to be randomised.
Participants	Women with a second trimester intrauterine fetal death.
Interventions	Vaginal misoprostol (200 mcg 4-hourly intervals) vs extra-amniotic PGF2alpha.
Outcomes	Bishop score, complete expulsion of placenta, oxytocin augmentation, examination under anaesthesia, side effects.
Notes	Abstract available only; results presented as percentage only.

Agrawal 2006

Methods	Stated to be randomised.
Participants	Women between 13 and 20 weeks' gestation; no other details provided.
Interventions	Misoprostol 200 mcg 3-hourly interval; oral, sublingual or vaginal.
Outcomes	Induction to delivery interval and 'success'.
Notes	Abstract available only; results presented as percentage only.

Nuthalapaty 2004

Methods	Stated to be "randomly assigned".
Participants	Women 14-24 weeks' gestation with medical or obstetric indications for termination of pregnancy.
Interventions	Vaginal misoprostol alone vs escalating oxytocin and vaginal misoprostol in combination.
Outcomes	Induction to delivery interval, "success", occurrence of side effects.
Notes	Abstract available only; results presented as percentage only.

Roy 2003

Methods	Stated to be double blind randomised trial.
Participants	Women 15 to 23 weeks' gestation undergoing termination for medical indications.
Interventions	Oral misoprostol (400 mcg 4-hourly intervals) vs vaginal misoprostol (600 mcg 12-hourly intervals).
Outcomes	Retained placenta, side effects.

Roy 2003 (*Continued*)

Notes	Abstract available only; results presented as percentage only.

Surita 1997

Methods	Stated to be "randomly allocated" and "blind".
Participants	Women greater than 15 weeks' gestation.
Interventions	Vaginal misoprostol vs laminaria.
Outcomes	Not stated.
Notes	Abstract available only; no results presented.

mcg: micrograms
vs: versus

DATA AND ANALYSES

Comparison 1. Vaginal misoprostol versus oral misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved in 24 hours	6	507	Risk Ratio (IV, Random, 95% CI)	0.37 [0.15, 0.87]
1.1 Low Dose Misoprostol	1	100	Risk Ratio (IV, Random, 95% CI)	0.18 [0.04, 0.78]
1.2 Moderate Dose Misoprostol	3	213	Risk Ratio (IV, Random, 95% CI)	0.24 [0.14, 0.42]
1.3 High Dose Misoprostol	2	194	Risk Ratio (IV, Random, 95% CI)	0.96 [0.05, 16.96]
3 Mean induction to birth interval	8	640	Mean Difference (IV, Random, 95% CI)	-5.54 [-8.92, -2.16]
3.1 Low Dose Misoprostol	3	208	Mean Difference (IV, Random, 95% CI)	-5.42 [-7.83, -1.00]
3.2 Moderate Dose Misoprostol	3	216	Mean Difference (IV, Random, 95% CI)	-6.53 [-12.59, -0.47]
3.3 High Dose Misoprostol	2	216	Mean Difference (IV, Random, 95% CI)	-3.60 [-20.38, 13.19]
5 Analgesia required	3	239	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.84, 1.57]
6 Surgical evacuation of the uterus	6	491	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.54, 1.14]
7 Vomiting	4	333	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.48, 1.07]
8 Nausea	3	273	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.42, 1.13]
9 Diarrhoea	5	413	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.24, 3.26]
10 Pyrexia	4	356	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.42, 1.30]

Comparison 2. Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved in 24 hours	2	363	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.62, 1.22]
2 Mean induction to birth interval	1	53	Mean Difference (IV, Fixed, 95% CI)	-4.70 [-11.19, 1.79]
3 Need for analgesia	3	416	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.86, 1.42]
4 Blood loss > 500 mL	1	279	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.30, 5.81]
5 Mean blood loss	1	53	Mean Difference (IV, Fixed, 95% CI)	85.0 [26.53, 143.47]
6 Need for blood transfusion	2	363	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [0.18, 21.65]
7 Surgical evacuation of the uterus	3	416	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.68, 1.13]
8 Nausea	1	279	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.75, 4.01]
9 Vomiting	3	416	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [1.09, 4.71]
10 Diarrhoea	3	416	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.73, 1.86]
11 Pyrexia	2	363	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.36, 2.42]

Comparison 3. Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved in 24 hours	3	235	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.64, 2.62]
2 Mean induction to delivery interval	2	109	Mean Difference (IV, Random, 95% CI)	2.22 [-14.44, 18.87]
3 Pain (VAS score greater than 5)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.62, 1.38]
4 Analgesia required	2	135	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.42, 1.53]
5 Mean blood loss	1	55	Mean Difference (IV, Fixed, 95% CI)	-61.0 [-145.71, 23.71]
6 Surgical evacuation of the uterus	3	235	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.55, 1.03]
7 Nausea	2	154	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.70, 1.86]
8 Vomiting	2	181	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.16, 4.62]
9 Diarrhoea	3	235	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.07, 3.15]
10 Pyrexia	2	154	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.13, 1.06]

Comparison 4. Vaginal misoprostol versus PGE2 (alone or with other agents)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved in 24 hours	4	251	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.36, 1.04]
1.1 Low Dose Misoprostol	2	109	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.44, 1.58]
1.2 Moderate Dose Misoprostol	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.13, 2.00]
1.3 High Dose Misoprostol	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.10, 1.14]
2 Mean induction to birth interval	4	165	Mean Difference (IV, Random, 95% CI)	-1.71 [-10.05, 6.63]
2.1 Low Dose Misoprostol	3	149	Mean Difference (IV, Random, 95% CI)	-1.00 [-9.53, 7.53]
2.2 Moderate Dose Misoprostol	1	16	Mean Difference (IV, Random, 95% CI)	-27.3 [-76.57, 21.97]
2.3 High Dose Misoprostol	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4 Analgesia required	4	315	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.11]
5 Blood loss > 500 mL	4	326	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.69, 10.78]
6 Need for blood transfusion	1	55	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Surgical evacuation of the uterus	5	380	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.20, 1.36]
8 Side effects - any	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.05, 2.40]
9 Nausea	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.35, 0.99]
10 Vomiting	4	254	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.31, 2.45]
11 Diarrhoea	3	261	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.06, 0.67]
12 Pyrexia	5	380	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.24, 3.20]

Comparison 5. Vaginal misoprostol versus PGF2alpha

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved in 24 hours	3	213	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.28, 4.06]
1.1 Low Dose Misoprostol	2	91	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.02, 26.21]
1.2 Moderate Dose Misoprostol	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 High Dose Misoprostol	1	122	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.50, 1.58]
2 Mean induction to birth interval	4	378	Mean Difference (IV, Random, 95% CI)	-2.84 [-6.06, 0.38]
2.1 Low Dose Misoprostol	2	91	Mean Difference (IV, Random, 95% CI)	-0.76 [-11.03, 9.51]
2.2 Moderate Dose Misoprostol	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
2.3 High Dose Misoprostol	2	287	Mean Difference (IV, Random, 95% CI)	-3.62 [-5.71, -1.53]
3 Blood loss > 500 mL	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.22, 2.20]
4 Need for blood transfusion	2	131	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Surgical evacuation of the uterus	5	439	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.41, 0.98]
6 Side effects - any	1	61	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.41, 2.59]
7 Nausea	3	338	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.47, 0.95]
8 Vomiting	4	378	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.42, 0.89]
9 Diarrhoea	5	458	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.15, 1.82]
10 Pyrexia	5	458	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.14, 3.61]

Comparison 6. Vaginal misoprostol versus vaginal misoprostol and oxytocin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean induction to birth interval	1	76	Mean Difference (IV, Fixed, 95% CI)	5.0 [-0.72, 10.72]
2 Surgical evacuation of the uterus	1	76	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.98, 3.90]
4 Vomiting	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.35, 1.93]
5 Diarrhoea	1	76	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.08, 18.05]
6 Pyrexia	1	76	Risk Ratio (M-H, Fixed, 95% CI)	2.34 [0.77, 7.13]

Comparison 7. Vaginal misoprostol versus glyceryl tri-nitrate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Need for analgesia	1	100	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [1.12, 4.40]
3 Blood loss > 500 mL	1	100	Risk Ratio (M-H, Fixed, 95% CI)	15.0 [0.88, 255.78]
4 Surgical evacuation of the uterus	1	100	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.50, 162.89]
5 Side effects - any	1	100	Risk Ratio (M-H, Fixed, 95% CI)	75.0 [4.73, 1188.67]
6 Vomiting	1	100	Risk Ratio (M-H, Fixed, 95% CI)	35.0 [2.16, 566.54]

7 Diarrhoea	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.92]
8 Pyrexia	1	100	Risk Ratio (M-H, Fixed, 95% CI)	31.0 [1.91, 504.35]

Comparison 8. Vaginal misoprostol versus vaginal misoprostol and laminaria

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved in 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.47, 1.97]
2 Blood loss > 500 mL	1	68	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Need for blood transfusion	1	68	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Vomiting	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.13, 3.97]
5 Diarrhoea	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.37]
6 Pyrexia	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.03, 1.72]

Comparison 9. Vaginal misoprostol versus vaginal misoprostol and nitric oxide donor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved in 24 hours	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.34, 2.33]
2 Mean induction to birth interval	1	61	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-8.01, 7.01]
3 Side effects - any	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.17, 1.07]

Comparison 10. Oral misoprostol versus PGF2alpha

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean induction to birth interval	1	133	Mean Difference (IV, Fixed, 95% CI)	9.40 [4.90, 13.90]
2 Surgical evacuation of the uterus	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.36, 1.69]
3 Nausea	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.56, 1.49]
4 Vomiting	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.56, 1.49]
5 Diarrhoea	1	133	Risk Ratio (M-H, Fixed, 95% CI)	2.60 [0.65, 10.41]
6 Pyrexia	1	133	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.57, 2.86]

Comparison 11. Combined oral and vaginal misoprostol versus vaginal misoprostol alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved in 24 hours	1	55	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.60, 5.50]
2 Mean induction to birth interval	1	43	Mean Difference (IV, Fixed, 95% CI)	5.20 [3.42, 6.98]
3 Need for analgesia	1	55	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.77, 1.39]
5 Surgical evacuation of the uterus	2	98	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.44, 1.57]
6 Nausea	1	55	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Vomiting	1	55	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Diarrhoea	1	55	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 12. Combined oral and vaginal misoprostol versus oral misoprostol alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved in 24 hours	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.96]
2 Need for analgesia	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.82, 1.55]
3 Surgical evacuation of the uterus	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.40, 1.85]
4 Nausea	1	56	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Vomiting	1	56	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Diarrhoea	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.83]

Comparison 13. Combined oral and vaginal misoprostol versus dilation and evacuation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea	1	18	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.56, 4.97]
2 Vomiting	1	18	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.48, 8.31]
3 Diarrhoea	1	18	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 14. Sublingual misoprostol versus vaginal misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved in 24 hours	2	202	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.08, 0.74]
2 Induction to delivery interval	2	202	Mean Difference (IV, Random, 95% CI)	-4.81 [-8.26, -1.37]
3 Analgesic requirements	1	102	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.43, 2.31]
4 Vomiting	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.35, 1.33]
5 Diarrhoea	1	102	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.51, 12.30]
6 Pyrexia	1	102	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.35, 2.89]

Comparison 15. Sublingual misoprostol versus oral misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved within 24 hours	2	204	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.01, 4.99]
2 Induction to delivery interval	2	202	Mean Difference (IV, Random, 95% CI)	-7.17 [-13.73, -0.60]
3 Analgesic requirements	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.31, 1.35]
4 Vomiting	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.42, 1.71]
5 Diarrhoea	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.27, 2.56]
6 Pyrexia	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.24, 1.53]

Comparison 16. Sublingual misoprostol 100 mcg versus sublingual misoprostol 200 mcg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to delivery interval	1	162	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-2.94, 2.00]
2 Vomiting	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.23, 1.28]
3 Diarrhoea	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.21, 1.83]
4 Pyrexia	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.32, 1.29]

Comparison 17. Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal birth not achieved in 24 hours	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.13, 3.03]
2 Pain (VAS score > 5)	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.47, 1.67]
3 Need for analgesia	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.73, 1.10]
4 Surgical evacuation of the uterus	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.33, 0.98]
5 Nausea	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.59, 1.59]
6 Vomiting	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.28, 1.17]
7 Diarrhoea	1	150	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [0.80, 6.39]
8 Vaginal birth not achieved in 24 hours	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 18. Vaginal misoprostol - moderate dose (cumulative dose 2400 mcg) versus high dose (cumulative dose 3200 mcg)

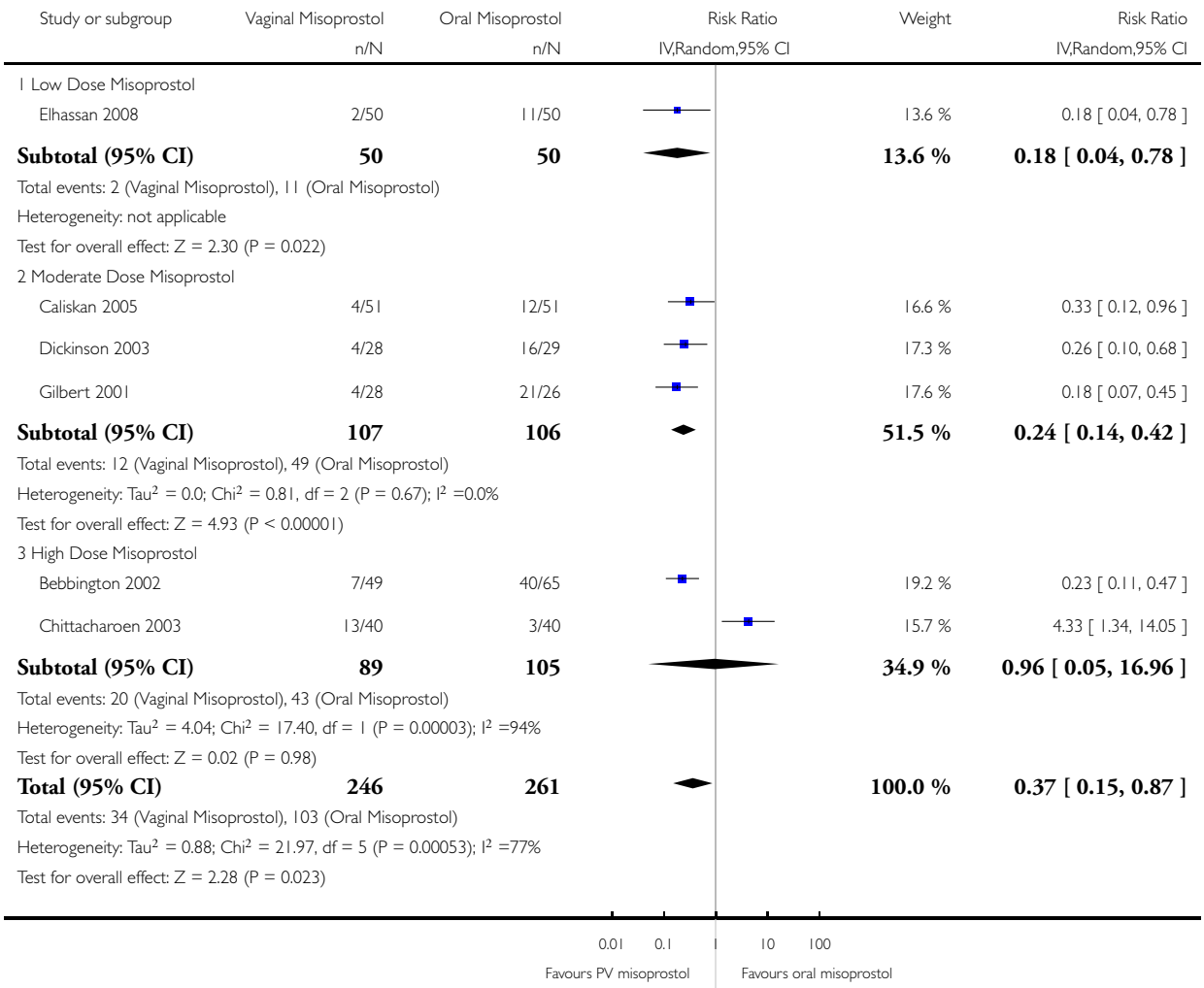
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean induction to birth interval	1	178	Mean Difference (IV, Fixed, 95% CI)	4.20 [1.36, 7.04]

Analysis 1.1. Comparison 1 Vaginal misoprostol versus oral misoprostol, Outcome 1 Vaginal birth not achieved in 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 1 Vaginal misoprostol versus oral misoprostol

Outcome: 1 Vaginal birth not achieved in 24 hours



Analysis 1.3. Comparison 1 Vaginal misoprostol versus oral misoprostol, Outcome 3 Mean induction to birth interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 1 Vaginal misoprostol versus oral misoprostol

Outcome: 3 Mean induction to birth interval

Study or subgroup	Vaginal Misoprostol N	Mean(SD)[hours]	Oral Misoprostol N	Mean(SD)[hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Low Dose Misoprostol							
Elhassan 2008	50	13.9 (5.1)	50	21 (10.5)		13.5 %	-7.10 [-10.34, -3.86]
Fadalla 2004	35	10.8 (2.8)	35	14.9 (3.4)		14.9 %	-4.10 [-5.56, -2.64]
Nyende 2004	20	13.5 (8.3)	18	21.4 (13.9)		8.9 %	-7.90 [-15.28, -0.52]
Subtotal (95% CI)	**105**		**103**			**37.3 %**	**-5.42 [-7.83, -3.00]**
Heterogeneity: $Tau^2 = 2.04$; $Chi^2 = 3.49$, df = 2 (P = 0.18); $I^2 = 43\%$							
Test for overall effect: Z = 4.39 (P = 0.000011)							
2 Moderate Dose Misoprostol							
Behrashi 2008	30	9.7 (4.2)	30	12.7 (7.3)		13.7 %	-3.00 [-6.01, 0.01]
Caliskan 2005	51	14.6 (8.3)	51	17.8 (10.6)		13.0 %	-3.20 [-6.89, 0.49]
Gilbert 2001	28	18.2 (9.9)	26	33 (11.4)		10.7 %	-14.80 [-20.51, -9.09]
Subtotal (95% CI)	**109**		**107**			**37.4 %**	**-6.53 [-12.59, -0.47]**
Heterogeneity: $Tau^2 = 24.14$; $Chi^2 = 13.86$, df = 2 (P = 0.00098); $I^2 = 86\%$							
Test for overall effect: Z = 2.11 (P = 0.035)							
3 High Dose Misoprostol							
Akoury 2004	84	18.3 (8.2)	52	30.5 (14.4)		12.3 %	-12.20 [-16.49, -7.91]
Chittacharoen 2003	40	18.88 (10.4)	40	13.95 (5.64)		13.0 %	4.93 [1.26, 8.60]
Subtotal (95% CI)	**124**		**92**			**25.3 %**	**-3.60 [-20.38, 13.19]**
Heterogeneity: $Tau^2 = 142.57$; $Chi^2 = 35.41$, df = 1 (P<0.00001); $I^2 = 97\%$							
Test for overall effect: Z = 0.42 (P = 0.67)							
Total (95% CI)	**338**		**302**			**100.0 %**	**-5.54 [-8.92, -2.16]**
Heterogeneity: $Tau^2 = 19.35$; $Chi^2 = 55.24$, df = 7 (P<0.00001); $I^2 = 87\%$							
Test for overall effect: Z = 3.21 (P = 0.0013)							

Analysis 1.5. Comparison 1 Vaginal misoprostol versus oral misoprostol, Outcome 5 Analgesia required.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 1 Vaginal misoprostol versus oral misoprostol

Outcome: 5 Analgesia required

Study or subgroup	Vaginal Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2005	14/51	9/51		23.3 %	1.56 [0.74, 3.27]
Chittacharoen 2003	9/40	10/40		25.9 %	0.90 [0.41, 1.98]
Dickinson 2003	21/28	20/29		50.8 %	1.09 [0.79, 1.50]
Total (95% CI)	**119**	**120**		**100.0 %**	**1.15 [0.84, 1.57]**

Total events: 44 (Vaginal Misoprostol), 39 (Oral Misoprostol)

Heterogeneity: Chi^2 = 1.12, df = 2 (P = 0.57); I^2 =0.0%

Test for overall effect: Z = 0.86 (P = 0.39)

Analysis 1.6. Comparison 1 Vaginal misoprostol versus oral misoprostol, Outcome 6 Surgical evacuation of the uterus.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 1 Vaginal misoprostol versus oral misoprostol

Outcome: 6 Surgical evacuation of the uterus

Study or subgroup	Vaginal Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	8/84	8/52		20.2 %	0.62 [0.25, 1.55]
Bebbington 2002	4/49	7/65		12.3 %	0.76 [0.23, 2.45]
Behrashi 2008	4/30	6/30		12.2 %	0.67 [0.21, 2.13]
Dickinson 2003	12/28	10/29		20.0 %	1.24 [0.64, 2.40]
Fadalla 2004	2/35	9/35		18.4 %	0.22 [0.05, 0.96]
Gilbert 2001	10/28	8/26		16.9 %	1.16 [0.54, 2.48]
Total (95% CI)	**254**	**237**		**100.0 %**	**0.79 [0.54, 1.14]**

Total events: 40 (Vaginal Misoprostol), 48 (Oral Misoprostol)

Heterogeneity: Chi^2 = 6.09, df = 5 (P = 0.30); I^2 =18%

Test for overall effect: Z = 1.28 (P = 0.20)

Analysis 1.7. Comparison 1 Vaginal misoprostol versus oral misoprostol, Outcome 7 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 1 Vaginal misoprostol versus oral misoprostol

Outcome: 7 Vomiting

Study or subgroup	Vaginal Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	18/84	17/52		0.66 [0.37, 1.15]
Caliskan 2005	13/51	16/51		0.81 [0.44, 1.51]
Dickinson 2003	0/28	0/29		0.0 [0.0, 0.0]
Nyende 2004	2/20	3/18		0.60 [0.11, 3.19]
Total (95% CI)	**183**	**150**		**0.71 [0.48, 1.07]**

Total events: 33 (Vaginal Misoprostol), 36 (Oral Misoprostol)

Heterogeneity: $Chi^2 = 0.30$, df = 2 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 1.63 (P = 0.10)

Analysis 1.8. Comparison 1 Vaginal misoprostol versus oral misoprostol, Outcome 8 Nausea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 1 Vaginal misoprostol versus oral misoprostol

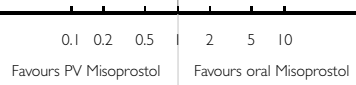
Outcome: 8 Nausea

Study or subgroup	Vaginal Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	22/84	20/52		0.68 [0.41, 1.12]
Chittacharoen 2003	1/40	1/40		1.00 [0.06, 15.44]
Dickinson 2003	0/28	0/29		0.0 [0.0, 0.0]
Total (95% CI)	**152**	**121**		**0.69 [0.42, 1.13]**

Total events: 23 (Vaginal Misoprostol), 21 (Oral Misoprostol)

Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%

Test for overall effect: Z = 1.46 (P = 0.14)



Analysis 1.9. Comparison 1 Vaginal misoprostol versus oral misoprostol, Outcome 9 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 1 Vaginal misoprostol versus oral misoprostol

Outcome: 9 Diarrhoea

Study or subgroup	Vaginal Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Akoury 2004	11/84	5/52		33.7 %	1.36 [0.50, 3.70]
Caliskan 2005	6/51	2/51		26.3 %	3.00 [0.64, 14.17]
Chittacharoen 2003	0/40	7/40		14.1 %	0.07 [0.00, 1.13]
Dickinson 2003	0/28	3/29		13.6 %	0.15 [0.01, 2.74]
Nyende 2004	1/20	0/18		12.3 %	2.71 [0.12, 62.70]
Total (95% CI)	**223**	**190**		**100.0 %**	**0.88 [0.24, 3.26]**

Total events: 18 (Vaginal Misoprostol), 17 (Oral Misoprostol)

Heterogeneity: Tau^2 = 1.06; Chi^2 = 8.36, df = 4 (P = 0.08); I^2 =52%

Test for overall effect: Z = 0.19 (P = 0.85)

Analysis 1.10. Comparison 1 Vaginal misoprostol versus oral misoprostol, Outcome 10 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 1 Vaginal misoprostol versus oral misoprostol

Outcome: 10 Pyrexia

Study or subgroup	Vaginal Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	9/84	9/52		45.9 %	0.62 [0.26, 1.46]
Caliskan 2005	10/51	6/51		24.7 %	1.67 [0.65, 4.24]
Chittacharoen 2003	0/40	4/40		18.6 %	0.11 [0.01, 2.00]
Nyende 2004	0/20	2/18		10.8 %	0.18 [0.01, 3.54]
Total (95% CI)	**195**	**161**		**100.0 %**	**0.74 [0.42, 1.30]**

Total events: 19 (Vaginal Misoprostol), 21 (Oral Misoprostol)

Heterogeneity: $Chi^2 = 5.59$, df = 3 (P = 0.13); $I^2 = 46\%$

Test for overall effect: Z = 1.06 (P = 0.29)

Analysis 2.1. Comparison 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval, Outcome 1 Vaginal birth not achieved in 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

Outcome: 1 Vaginal birth not achieved in 24 hours

Study or subgroup	6-hourly interval n/N	12-hourly interval n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herabutya 2005	37/140	46/139		89.2 %	0.80 [0.56, 1.15]
Jain 1996	9/47	5/37		10.8 %	1.42 [0.52, 3.87]
Total (95% CI)	**187**	**176**		**100.0 %**	**0.87 [0.62, 1.22]**

Total events: 46 (6-hourly interval), 51 (12-hourly interval)

Heterogeneity: $Chi^2 = 1.11$, df = 1 (P = 0.29); $I^2 = 10\%$

Test for overall effect: Z = 0.83 (P = 0.41)

Analysis 2.2. Comparison 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval, Outcome 2 Mean induction to birth interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

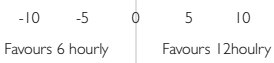
Comparison: 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

Outcome: 2 Mean induction to birth interval

Study or subgroup	6-hourly interval N	Mean(SD)[hours]	12-hourly interval N	Mean(SD)[hours]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Nuutila 1997	27	23.1 (12.3)	26	27.8 (11.8)		100.0 %	-4.70 [-11.19, 1.79]
Total (95% CI)	**27**		**26**			**100.0 %**	**-4.70 [-11.19, 1.79]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.42 (P = 0.16)



Analysis 2.3. Comparison 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval, Outcome 3 Need for analgesia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

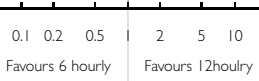
Outcome: 3 Need for analgesia

Study or subgroup	6-hourly interval n/N	12-hourly interval n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herabutya 2005	47/140	39/139		54.7 %	1.20 [0.84, 1.70]
Jain 1996	23/47	18/37		28.2 %	1.01 [0.65, 1.56]
Nuutila 1997	12/27	12/26		17.1 %	0.96 [0.53, 1.74]
Total (95% CI)	**214**	**202**		**100.0 %**	**1.10 [0.86, 1.42]**

Total events: 82 (6-hourly interval), 69 (12-hourly interval)

Heterogeneity: Chi^2 = 0.57, df = 2 (P = 0.75); I^2 =0.0%

Test for overall effect: Z = 0.76 (P = 0.45)



Analysis 2.4. Comparison 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval, Outcome 4 Blood loss > 500 mL.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

Outcome: 4 Blood loss > 500 mL

Study or subgroup	6-hourly interval n/N	12-hourly interval n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herabutya 2005	4/140	3/139		100.0 %	1.32 [0.30, 5.81]
Total (95% CI)	**140**	**139**		**100.0 %**	**1.32 [0.30, 5.81]**
Total events: 4 (6-hourly interval), 3 (12-hourly interval)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					

Analysis 2.5. Comparison 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval, Outcome 5 Mean blood loss.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

Outcome: 5 Mean blood loss

Study or subgroup	6-hourly interval N	Mean(SD)	12-hourly interval N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Nuutila 1997	27	287 (136)	26	202 (73)		100.0 %	85.00 [26.53, 143.47]
Total (95% CI)	**27**		**26**			**100.0 %**	**85.00 [26.53, 143.47]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.85 (P = 0.0044)							

Analysis 2.6. Comparison 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval, Outcome 6 Need for blood transfusion.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

Outcome: 6 Need for blood transfusion

Study or subgroup	6-hourly interval n/N	12-hourly interval n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Herabutya 2005	2/140	1/139		1.99 [0.18, 21.65]
Jain 1996	0/47	0/37		0.0 [0.0, 0.0]
Total (95% CI)	**187**	**176**		**1.99 [0.18, 21.65]**

Total events: 2 (6-hourly interval), 1 (12-hourly interval)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.56 (P = 0.57)

Analysis 2.7. Comparison 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval, Outcome 7 Surgical evacuation of the uterus.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

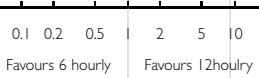
Outcome: 7 Surgical evacuation of the uterus

Study or subgroup	6-hourly interval n/N	12-hourly interval n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herabutya 2005	39/140	46/139		58.5 %	0.84 [0.59, 1.20]
Jain 1996	23/47	22/37		31.2 %	0.82 [0.55, 1.22]
Nuutila 1997	10/27	8/26		10.3 %	1.20 [0.56, 2.57]
Total (95% CI)	**214**	**202**		**100.0 %**	**0.87 [0.68, 1.13]**

Total events: 72 (6-hourly interval), 76 (12-hourly interval)

Heterogeneity: $Chi^2 = 0.82$, df = 2 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 1.04 (P = 0.30)



Analysis 2.8. Comparison 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval, Outcome 8 Nausea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

Outcome: 8 Nausea

Study or subgroup	6-hourly interval n/N	12-hourly interval n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herabutya 2005	14/140	8/139		100.0 %	1.74 [0.75, 4.01]
Total (95% CI)	**140**	**139**		**100.0 %**	**1.74 [0.75, 4.01]**
Total events: 14 (6-hourly interval), 8 (12-hourly interval)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.29 (P = 0.20)					

Analysis 2.9. Comparison 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval, Outcome 9 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

Outcome: 9 Vomiting

Study or subgroup	6-hourly interval n/N	12-hourly interval n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herabutya 2005	12/140	6/139		62.5 %	1.99 [0.77, 5.14]
Jain 1996	4/47	0/37		5.8 %	7.13 [0.40, 128.28]
Nuutila 1997	6/27	3/26		31.7 %	1.93 [0.54, 6.91]
Total (95% CI)	**214**	**202**		**100.0 %**	**2.26 [1.09, 4.71]**
Total events: 22 (6-hourly interval), 9 (12-hourly interval)					
Heterogeneity: Chi^2 = 0.74, df = 2 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 2.18 (P = 0.029)					

Analysis 2.10. Comparison 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval, Outcome 10 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

Outcome: 10 Diarrhoea

Study or subgroup	6-hourly interval n/N	12-hourly interval n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Herabutya 2005	55/140	48/139		90.6 %	1.23 [0.75, 2.00]
Jain 1996	1/47	0/37		1.7 %	2.42 [0.10, 61.12]
Nuutila 1997	0/27	2/26		7.7 %	0.18 [0.01, 3.90]
Total (95% CI)	**214**	**202**		**100.0 %**	**1.17 [0.73, 1.86]**

Total events: 56 (6-hourly interval), 50 (12-hourly interval)

Heterogeneity: Chi^2 = 1.66, df = 2 (P = 0.44); I^2 =0.0%

Test for overall effect: Z = 0.64 (P = 0.52)

Analysis 2.11. Comparison 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval, Outcome 11 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 2 Vaginal misoprostol - 6-hourly versus 12-hourly dosing interval

Outcome: 11 Pyrexia

Study or subgroup	6-hourly interval n/N	12-hourly interval n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herabutya 2005	74/140	43/139		92.8 %	1.71 [1.27, 2.29]
Jain 1996	12/47	3/37		7.2 %	3.15 [0.96, 10.35]
Total (95% CI)	**187**	**176**		**100.0 %**	**1.81 [1.36, 2.42]**

Total events: 86 (6-hourly interval), 46 (12-hourly interval)

Heterogeneity: Chi^2 = 0.98, df = 1 (P = 0.32); I^2 =0.0%

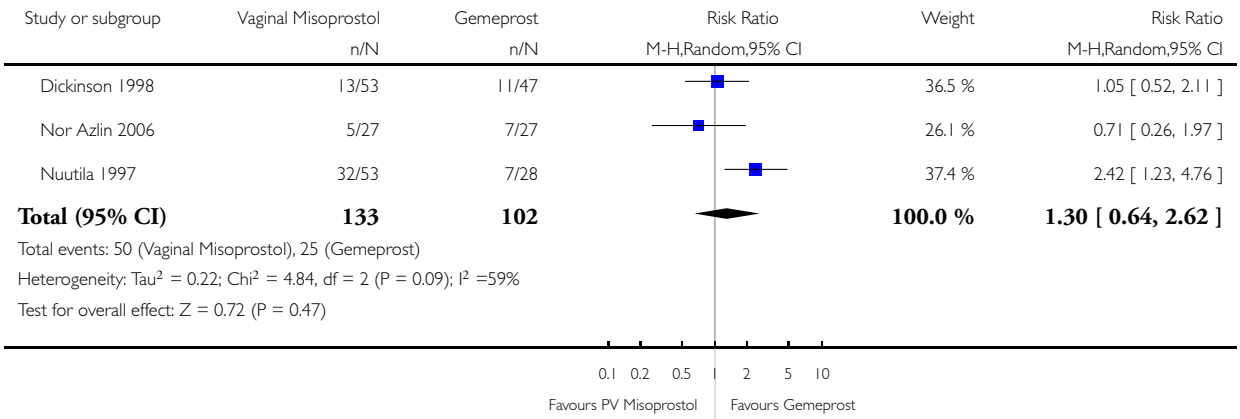
Test for overall effect: Z = 4.05 (P = 0.000051)

Analysis 3.1. Comparison 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin), Outcome 1 Vaginal birth not achieved in 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin)

Outcome: 1 Vaginal birth not achieved in 24 hours

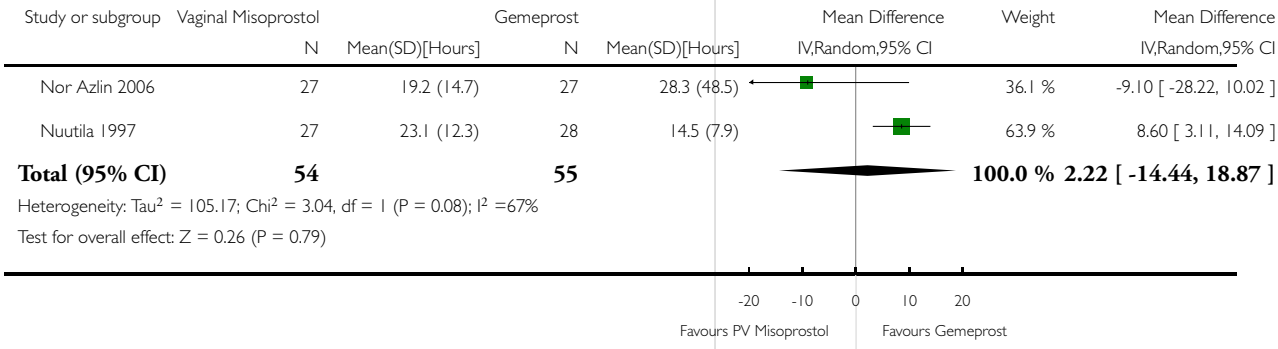


Analysis 3.2. Comparison 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin), Outcome 2 Mean induction to delivery interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin)

Outcome: 2 Mean induction to delivery interval



Analysis 3.3. Comparison 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin), Outcome 3 Pain (VAS score greater than 5).

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin)

Outcome: 3 Pain (VAS score greater than 5)

Study or subgroup	Vaginal Misoprostol n/N	Gemeprost n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 1998	25/53	24/47		100.0 %	0.92 [0.62, 1.38]
Total (95% CI)	**53**	**47**		**100.0 %**	**0.92 [0.62, 1.38]**
Total events: 25 (Vaginal Misoprostol), 24 (Gemeprost)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.39 (P = 0.70)					

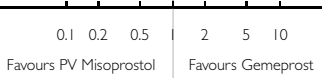
Analysis 3.4. Comparison 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin), Outcome 4 Analgesia required.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin)

Outcome: 4 Analgesia required

Study or subgroup	Vaginal Misoprostol n/N	Gemeprost n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Nor Azlin 2006	21/27	19/27		50.7 %	1.11 [0.80, 1.52]
Nuutila 1997	24/53	22/28		49.3 %	0.58 [0.40, 0.82]
Total (95% CI)	**80**	**55**		**100.0 %**	**0.80 [0.42, 1.53]**
Total events: 45 (Vaginal Misoprostol), 41 (Gemeprost)					
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 7.39$, df = 1 (P = 0.01); $I^2 = 86\%$					
Test for overall effect: Z = 0.67 (P = 0.50)					



Analysis 3.5. Comparison 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin), Outcome 5 Mean blood loss.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin)

Outcome: 5 Mean blood loss

Study or subgroup	Vaginal Misoprostol N	Mean(SD)	Gemeprost N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Nuutila 1997	27	287 (136)	28	348 (182)		100.0 %	-61.00 [-145.71, 23.71]
Total (95% CI)	**27**		**28**			**100.0 %**	**-61.00 [-145.71, 23.71]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.41 (P = 0.16)

Analysis 3.6. Comparison 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin), Outcome 6 Surgical evacuation of the uterus.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin)

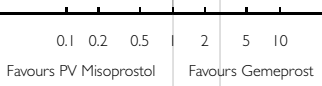
Outcome: 6 Surgical evacuation of the uterus

Study or subgroup	Vaginal Misoprostol n/N	Gemeprost n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 1998	20/53	20/47		40.7 %	0.89 [0.55, 1.43]
Nor Azlin 2006	8/27	10/27		19.2 %	0.80 [0.37, 1.71]
Nuutila 1997	18/53	16/28		40.2 %	0.59 [0.36, 0.97]
Total (95% CI)	**133**	**102**		**100.0 %**	**0.75 [0.55, 1.03]**

Total events: 46 (Vaginal Misoprostol), 46 (Gemeprost)

Heterogeneity: Chi^2 = 1.35, df = 2 (P = 0.51); I^2 =0.0%

Test for overall effect: Z = 1.77 (P = 0.076)



Analysis 3.7. Comparison 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin), Outcome 7 Nausea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin)

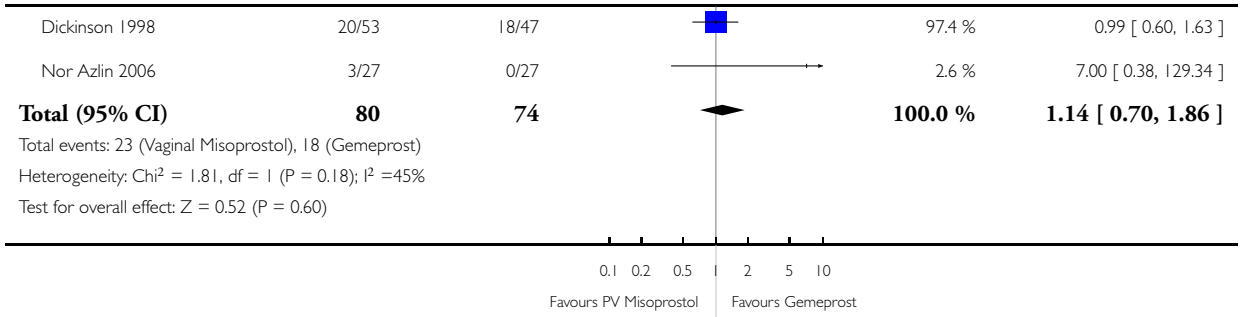
Outcome: 7 Nausea

Study or subgroup	Vaginal Misoprostol n/N	Gemeprost n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 1998	20/53	18/47		97.4 %	0.99 [0.60, 1.63]
Nor Azlin 2006	3/27	0/27		2.6 %	7.00 [0.38, 129.34]
Total (95% CI)	**80**	**74**		**100.0 %**	**1.14 [0.70, 1.86]**

Total events: 23 (Vaginal Misoprostol), 18 (Gemeprost)

Heterogeneity: Chi^2 = 1.81, df = 1 (P = 0.18); I^2 =45%

Test for overall effect: Z = 0.52 (P = 0.60)



Analysis 3.8. Comparison 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin), Outcome 8 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin)

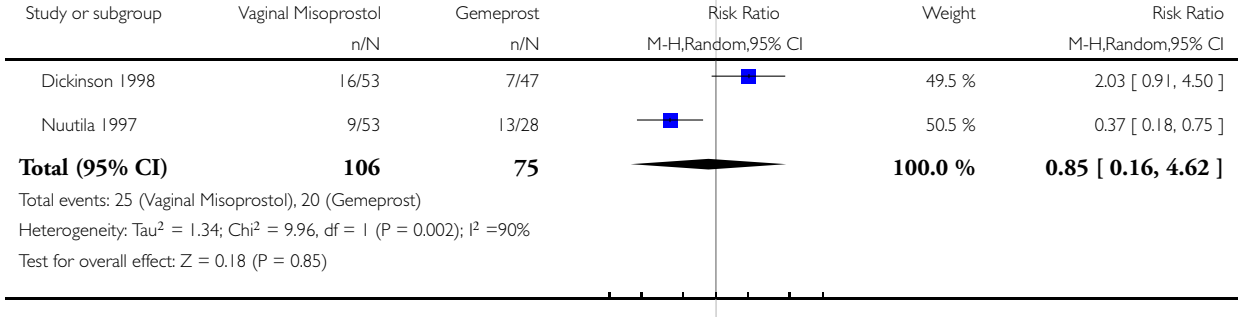
Outcome: 8 Vomiting

Study or subgroup	Vaginal Misoprostol n/N	Gemeprost n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dickinson 1998	16/53	7/47		49.5 %	2.03 [0.91, 4.50]
Nuutila 1997	9/53	13/28		50.5 %	0.37 [0.18, 0.75]
Total (95% CI)	**106**	**75**		**100.0 %**	**0.85 [0.16, 4.62]**

Total events: 25 (Vaginal Misoprostol), 20 (Gemeprost)

Heterogeneity: Tau^2 = 1.34; Chi^2 = 9.96, df = 1 (P = 0.002); I^2 =90%

Test for overall effect: Z = 0.18 (P = 0.85)



Analysis 3.9. Comparison 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin), Outcome 9 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin)

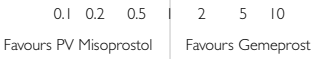
Outcome: 9 Diarrhoea

Study or subgroup	Vaginal Misoprostol n/N	Gemeprost n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dickinson 1998	1/53	1/47		26.1 %	0.89 [0.06, 13.79]
Nor Azlin 2006	2/27	1/27		30.7 %	2.00 [0.19, 20.77]
Nuutila 1997	2/53	9/28		43.1 %	0.12 [0.03, 0.51]
Total (95% CI)	**133**	**102**		**100.0 %**	**0.48 [0.07, 3.15]**

Total events: 5 (Vaginal Misoprostol), 11 (Gemeprost)

Heterogeneity: $Tau^2 = 1.60$; $Chi^2 = 4.69$, df = 2 (P = 0.10); $I^2 = 57\%$

Test for overall effect: Z = 0.77 (P = 0.44)



Analysis 3.10. Comparison 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin), Outcome 10 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 3 Vaginal misoprostol versus Gemeprost (PGE1) (alone or with oxytocin)

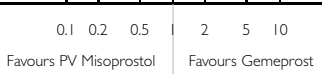
Outcome: 10 Pyrexia

Study or subgroup	Vaginal Misoprostol n/N	Gemeprost n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dickinson 1998	11/53	18/47		66.4 %	0.54 [0.29, 1.03]
Nor Azlin 2006	2/27	11/27		33.6 %	0.18 [0.04, 0.74]
Total (95% CI)	**80**	**74**		**100.0 %**	**0.38 [0.13, 1.06]**

Total events: 13 (Vaginal Misoprostol), 29 (Gemeprost)

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 2.01$, df = 1 (P = 0.16); $I^2 = 50\%$

Test for overall effect: Z = 1.85 (P = 0.064)



Analysis 4.1. Comparison 4 Vaginal misoprostol versus PGE2 (alone or with other agents), Outcome 1 Vaginal birth not achieved in 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 4 Vaginal misoprostol versus PGE2 (alone or with other agents)

Outcome: 1 Vaginal birth not achieved in 24 hours

Study or subgroup	Vaginal Misoprostol n/N	PGE2 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low Dose Misoprostol					
Herabutya 1997	9/29	9/25		34.2 %	0.86 [0.41, 1.83]
Jain 1999	4/28	5/27		18.0 %	0.77 [0.23, 2.57]
Subtotal (95% CI)	**57**	**52**		**52.2 %**	**0.83 [0.44, 1.58]**
Total events: 13 (Vaginal Misoprostol), 14 (PGE2)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 0.57 (P = 0.57)					
2 Moderate Dose Misoprostol					
Jansen 2008	2/8	4/8		14.1 %	0.50 [0.13, 2.00]
Subtotal (95% CI)	**8**	**8**		**14.1 %**	**0.50 [0.13, 2.00]**
Total events: 2 (Vaginal Misoprostol), 4 (PGE2)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
3 High Dose Misoprostol					
Ramsey 2004	3/60	10/66		33.7 %	0.33 [0.10, 1.14]
Subtotal (95% CI)	**60**	**66**		**33.7 %**	**0.33 [0.10, 1.14]**
Total events: 3 (Vaginal Misoprostol), 10 (PGE2)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.080)					
Total (95% CI)	**125**	**126**		**100.0 %**	**0.62 [0.36, 1.04]**
Total events: 18 (Vaginal Misoprostol), 28 (PGE2)					
Heterogeneity: Chi^2 = 1.96, df = 3 (P = 0.58); I^2 =0.0%					
Test for overall effect: Z = 1.81 (P = 0.070)					

Analysis 4.2. Comparison 4 Vaginal misoprostol versus PGE2 (alone or with other agents), Outcome 2 Mean induction to birth interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 4 Vaginal misoprostol versus PGE2 (alone or with other agents)

Outcome: 2 Mean induction to birth interval

Study or subgroup	Vaginal Misoprostol N	Mean(SD)[Hours]	PGE2 N	Mean(SD)[Hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Low Dose Misoprostol							
Herabutya 1997	29	24.3 (21.5)	25	23 (15.9)		25.1 %	1.30 [-8.70, 11.30]
Kara 1999	32	5.4 (0.5)	33	12.5 (7.6)		37.8 %	-7.10 [-9.70, -4.50]
Owen 1999	15	22 (7.3)	15	18 (6.6)		34.4 %	4.00 [-0.98, 8.98]
Subtotal (95% CI)	**76**		**73**			**97.3 %**	**-1.00 [-9.53, 7.53]**
Heterogeneity: $Tau^2 = 47.09$; $Chi^2 = 16.32$, df = 2 (P = 0.00029); $I^2 = 88\%$							
Test for overall effect: Z = 0.23 (P = 0.82)							
2 Moderate Dose Misoprostol							
Jansen 2008	8	17.8 (15.9)	8	45.1 (69.3)		2.7 %	-27.30 [-76.57, 21.97]
Subtotal (95% CI)	**8**		**8**			**2.7 %**	**-27.30 [-76.57, 21.97]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.09 (P = 0.28)							
3 High Dose Misoprostol							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**84**		**81**			**100.0 %**	**-1.71 [-10.05, 6.63]**
Heterogeneity: $Tau^2 = 46.14$; $Chi^2 = 17.15$, df = 3 (P = 0.00066); $I^2 = 83\%$							
Test for overall effect: Z = 0.40 (P = 0.69)							

Analysis 4.4. Comparison 4 Vaginal misoprostol versus PGE2 (alone or with other agents), Outcome 4 Analgesia required.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 4 Vaginal misoprostol versus PGE2 (alone or with other agents)

Outcome: 4 Analgesia required

Study or subgroup	Vaginal Misoprostol n/N	PGE2 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herabutya 1997	10/29	11/25		15.4 %	0.78 [0.40, 1.53]
Jain 1999	16/28	18/27		23.9 %	0.86 [0.56, 1.30]
Makhlouf 2003	20/50	9/30		14.7 %	1.33 [0.70, 2.54]
Ramsey 2004	26/60	37/66		46.0 %	0.77 [0.54, 1.11]
Total (95% CI)	**167**	**148**		**100.0 %**	**0.88 [0.69, 1.11]**

Total events: 72 (Vaginal Misoprostol), 75 (PGE2)

Heterogeneity: Chi^2 = 2.22, df = 3 (P = 0.53); I^2 =0.0%

Test for overall effect: Z = 1.08 (P = 0.28)

Analysis 4.5. Comparison 4 Vaginal misoprostol versus PGE2 (alone or with other agents), Outcome 5 Blood loss > 500 mL.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 4 Vaginal misoprostol versus PGE2 (alone or with other agents)

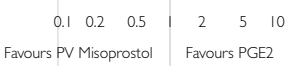
Outcome: 5 Blood loss > 500 mL

Study or subgroup	Vaginal Misoprostol n/N	PGE2 n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Jain 1999	0/28	0/27		0.0 [0.0, 0.0]
Kara 1999	1/32	0/33		3.09 [0.13, 73.19]
Makhlouf 2003	7/50	0/30		9.12 [0.54, 154.15]
Ramsey 2004	1/60	2/66		0.55 [0.05, 5.91]
Total (95% CI)	**170**	**156**		**2.73 [0.69, 10.78]**

Total events: 9 (Vaginal Misoprostol), 2 (PGE2)

Heterogeneity: Chi^2 = 2.45, df = 2 (P = 0.29); I^2 =18%

Test for overall effect: Z = 1.43 (P = 0.15)



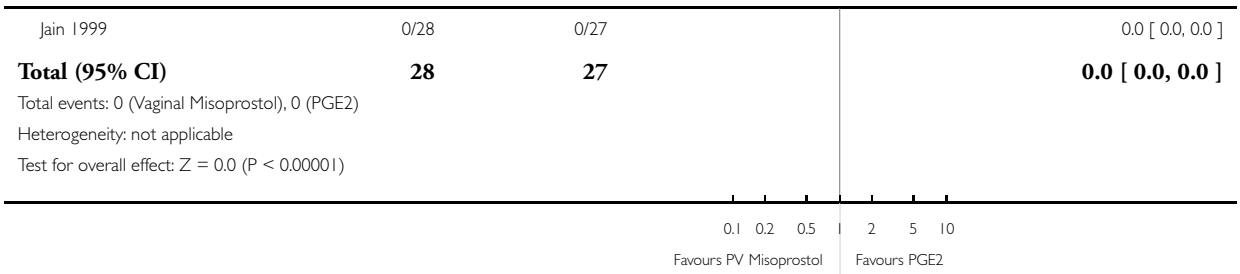
Analysis 4.6. Comparison 4 Vaginal misoprostol versus PGE2 (alone or with other agents), Outcome 6 Need for blood transfusion.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 4 Vaginal misoprostol versus PGE2 (alone or with other agents)

Outcome: 6 Need for blood transfusion

Study or subgroup	Vaginal Misoprostol n/N	PGE2 n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Jain 1999	0/28	0/27		0.0 [0.0, 0.0]
Total (95% CI)	**28**	**27**		**0.0 [0.0, 0.0]**
Total events: 0 (Vaginal Misoprostol), 0 (PGE2)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



Analysis 4.7. Comparison 4 Vaginal misoprostol versus PGE2 (alone or with other agents), Outcome 7 Surgical evacuation of the uterus.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 4 Vaginal misoprostol versus PGE2 (alone or with other agents)

Outcome: 7 Surgical evacuation of the uterus

Study or subgroup	Vaginal Misoprostol n/N	PGE2 n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Herabutya 1997	3/29	7/25		21.7 %	0.37 [0.11, 1.28]
Jain 1999	16/28	15/27		31.7 %	1.03 [0.65, 1.64]
Kara 1999	4/32	13/33		24.8 %	0.32 [0.12, 0.87]
Makhlouf 2003	4/50	0/30		8.3 %	5.47 [0.30, 98.18]
Ramsey 2004	1/60	10/66		13.5 %	0.11 [0.01, 0.83]
Total (95% CI)	**199**	**181**		**100.0 %**	**0.52 [0.20, 1.36]**

Total events: 28 (Vaginal Misoprostol), 45 (PGE2)

Heterogeneity: $Tau^2 = 0.69$; $Chi^2 = 12.39$, df = 4 (P = 0.01); $I^2 = 68\%$

Test for overall effect: Z = 1.33 (P = 0.18)

Analysis 4.8. Comparison 4 Vaginal misoprostol versus PGE2 (alone or with other agents), Outcome 8 Side effects - any.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 4 Vaginal misoprostol versus PGE2 (alone or with other agents)

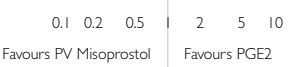
Outcome: 8 Side effects - any

Study or subgroup	Vaginal Misoprostol n/N	PGE2 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Makhlouf 2003	37/50	14/30		100.0 %	1.59 [1.05, 2.40]
Total (95% CI)	**50**	**30**		**100.0 %**	**1.59 [1.05, 2.40]**

Total events: 37 (Vaginal Misoprostol), 14 (PGE2)

Heterogeneity: not applicable

Test for overall effect: Z = 2.17 (P = 0.030)



Analysis 4.9. Comparison 4 Vaginal misoprostol versus PGE2 (alone or with other agents), Outcome 9 Nausea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 4 Vaginal misoprostol versus PGE2 (alone or with other agents)

Outcome: 9 Nausea

Study or subgroup	Vaginal Misoprostol n/N	PGE2 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ramsey 2004	15/60	28/66		100.0 %	0.59 [0.35, 0.99]
Total (95% CI)	**60**	**66**		**100.0 %**	**0.59 [0.35, 0.99]**
Total events: 15 (Vaginal Misoprostol), 28 (PGE2)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.99 (P = 0.046)					

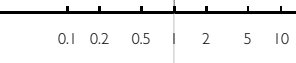
Analysis 4.10. Comparison 4 Vaginal misoprostol versus PGE2 (alone or with other agents), Outcome 10 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 4 Vaginal misoprostol versus PGE2 (alone or with other agents)

Outcome: 10 Vomiting

Study or subgroup	Vaginal Misoprostol n/N	PGE2 n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Herabutya 1997	3/29	1/25		15.2 %	2.59 [0.29, 23.32]
Jain 1999	1/28	9/27		17.3 %	0.11 [0.01, 0.79]
Kara 1999	4/32	4/33		27.6 %	1.03 [0.28, 3.78]
Makhlouf 2003	17/50	8/30		39.9 %	1.28 [0.63, 2.59]
Total (95% CI)	**139**	**115**		**100.0 %**	**0.87 [0.31, 2.45]**
Total events: 25 (Vaginal Misoprostol), 22 (PGE2)					
Heterogeneity: Tau^2 = 0.57; Chi^2 = 6.45, df = 3 (P = 0.09); I^2 =54%					
Test for overall effect: Z = 0.26 (P = 0.80)					



Analysis 4.11. Comparison 4 Vaginal misoprostol versus PGE2 (alone or with other agents), Outcome 11 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 4 Vaginal misoprostol versus PGE2 (alone or with other agents)

Outcome: 11 Diarrhoea

Study or subgroup	Vaginal Misoprostol n/N	PGE2 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jain 1999	1/28	8/27		52.8 %	0.12 [0.02, 0.90]
Makhlouf 2003	1/50	0/30		4.0 %	1.82 [0.08, 43.38]
Ramsey 2004	1/60	7/66		43.2 %	0.16 [0.02, 1.24]
Total (95% CI)	**138**	**123**		**100.0 %**	**0.20 [0.06, 0.67]**

Total events: 3 (Vaginal Misoprostol), 15 (PGE2)

Heterogeneity: $Chi^2 = 2.16$, df = 2 (P = 0.34); $I^2 = 7\%$

Test for overall effect: Z = 2.61 (P = 0.00911)

Analysis 4.12. Comparison 4 Vaginal misoprostol versus PGE2 (alone or with other agents), Outcome 12 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 4 Vaginal misoprostol versus PGE2 (alone or with other agents)

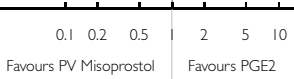
Outcome: 12 Pyrexia

Study or subgroup	Vaginal Misoprostol n/N	PGE2 n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Herabutya 1997	0/29	1/25		10.6 %	0.29 [0.01, 6.79]
Jain 1999	3/28	17/27		23.7 %	0.17 [0.06, 0.52]
Kara 1999	1/32	1/33		12.6 %	1.03 [0.07, 15.79]
Makhlouf 2003	15/50	6/30		25.6 %	1.50 [0.65, 3.45]
Ramsey 2004	40/60	14/66		27.5 %	3.14 [1.91, 5.17]
Total (95% CI)	**199**	**181**		**100.0 %**	**0.88 [0.24, 3.20]**

Total events: 59 (Vaginal Misoprostol), 39 (PGE2)

Heterogeneity: $Tau^2 = 1.51$; $Chi^2 = 24.96$, df = 4 (P = 0.00005); $I^2 = 84\%$

Test for overall effect: Z = 0.19 (P = 0.85)

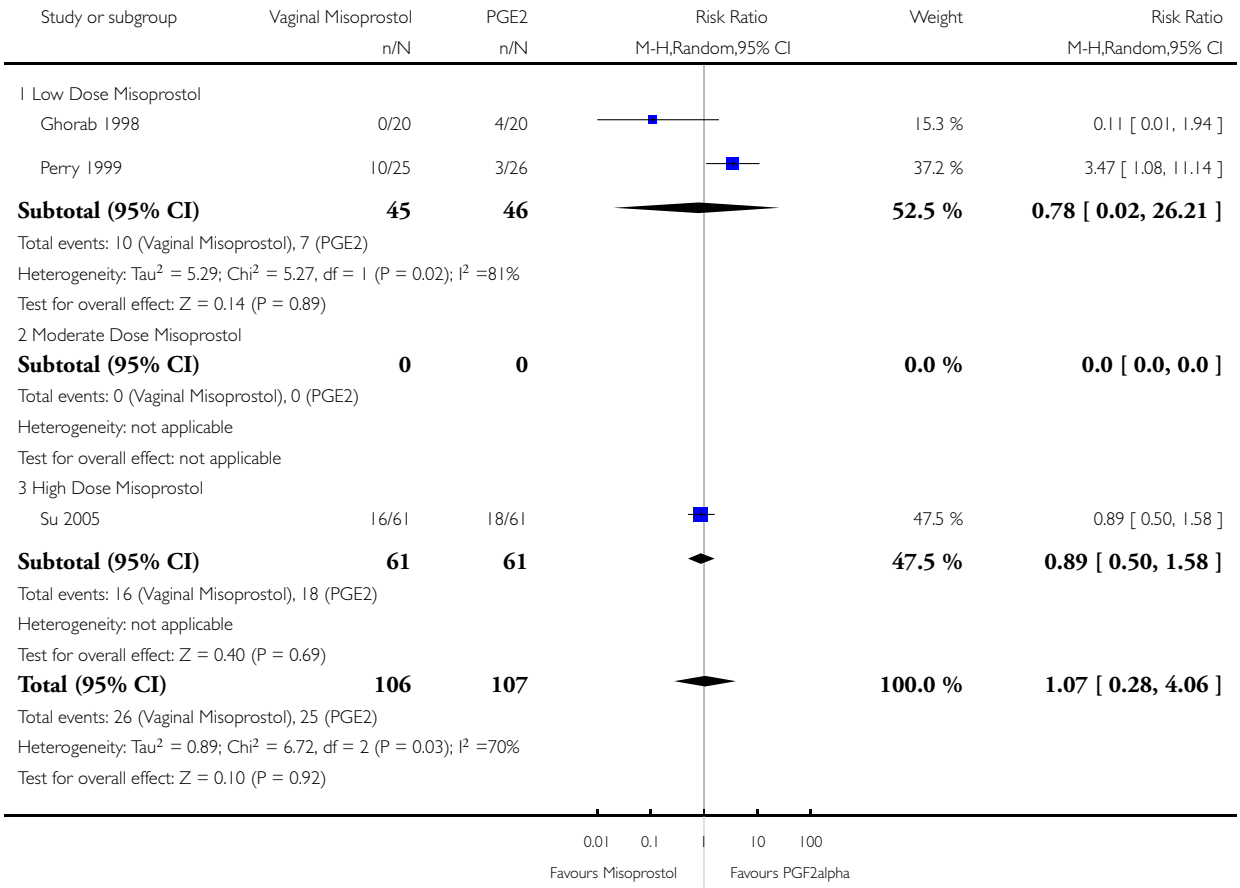


Analysis 5.1. Comparison 5 Vaginal misoprostol versus PGF2alpha, Outcome 1 Vaginal birth not achieved in 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 5 Vaginal misoprostol versus PGF2alpha

Outcome: 1 Vaginal birth not achieved in 24 hours



Analysis 5.2. Comparison 5 Vaginal misoprostol versus PGF2alpha, Outcome 2 Mean induction to birth interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 5 Vaginal misoprostol versus PGF2alpha

Outcome: 2 Mean induction to birth interval

Study or subgroup	Vaginal Misoprostol N	Mean(SD)[Hours]	PGF2alpha N	Mean(SD)[Hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Low Dose Misoprostol							
Ghorab 1998	20	10.3 (4)	20	16 (5.9)		27.4 %	-5.70 [-8.82, -2.58]
Perry 1999	25	22.3 (12.5)	26	17.5 (8.6)		16.4 %	4.80 [-1.11, 10.71]
Subtotal (95% CI)	**45**		**46**			**43.8 %**	**-0.76 [-11.03, 9.51]**
Heterogeneity: $Tau^2 = 49.31$; $Chi^2 = 9.48$, df = 1 (P = 0.002); $I^2 = 89\%$							
Test for overall effect: Z = 0.15 (P = 0.88)							
2 Moderate Dose Misoprostol							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 High Dose Misoprostol							
Akoury 2004	84	18.3 (8.2)	81	21.1 (10.2)		28.7 %	-2.80 [-5.63, 0.03]
Su 2005	61	16.2 (8.3)	61	20.8 (9.1)		27.5 %	-4.60 [-7.69, -1.51]
Subtotal (95% CI)	**145**		**142**			**56.2 %**	**-3.62 [-5.71, -1.53]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.71$, df = 1 (P = 0.40); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.40 (P = 0.00067)							
Total (95% CI)	**190**		**188**			**100.0 %**	**-2.84 [-6.06, 0.38]**
Heterogeneity: $Tau^2 = 7.33$; $Chi^2 = 10.20$, df = 3 (P = 0.02); $I^2 = 71\%$							
Test for overall effect: Z = 1.73 (P = 0.084)							

Analysis 5.3. Comparison 5 Vaginal misoprostol versus PGF2alpha, Outcome 3 Blood loss > 500 mL.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 5 Vaginal misoprostol versus PGF2alpha

Outcome: 3 Blood loss > 500 mL

Study or subgroup	Vaginal Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Munthali 2001	4/30	6/31		100.0 %	0.69 [0.22, 2.20]
Total (95% CI)	**30**	**31**		**100.0 %**	**0.69 [0.22, 2.20]**
Total events: 4 (Vaginal Misoprostol), 6 (PGF2alpha)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					

Analysis 5.4. Comparison 5 Vaginal misoprostol versus PGF2alpha, Outcome 4 Need for blood transfusion.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 5 Vaginal misoprostol versus PGF2alpha

Outcome: 4 Need for blood transfusion

Study or subgroup	Vaginal Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Perry 1999	0/25	0/26		0.0 [0.0, 0.0]
Zuo 1998	0/40	0/40		0.0 [0.0, 0.0]
Total (95% CI)	**65**	**66**		**0.0 [0.0, 0.0]**
Total events: 0 (Vaginal Misoprostol), 0 (PGF2alpha)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 5.5. Comparison 5 Vaginal misoprostol versus PGF2alpha, Outcome 5 Surgical evacuation of the uterus.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 5 Vaginal misoprostol versus PGF2alpha

Outcome: 5 Surgical evacuation of the uterus

Study or subgroup	Vaginal Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	8/84	16/81		36.9 %	0.48 [0.22, 1.06]
Ghorab 1998	3/20	7/20		15.9 %	0.43 [0.13, 1.43]
Munthali 2001	5/30	6/31		13.4 %	0.86 [0.29, 2.52]
Perry 1999	2/25	3/26		6.7 %	0.69 [0.13, 3.81]
Su 2005	10/61	12/61		27.2 %	0.83 [0.39, 1.78]
Total (95% CI)	**220**	**219**		**100.0 %**	**0.63 [0.41, 0.98]**

Total events: 28 (Vaginal Misoprostol), 44 (PGF2alpha)

Heterogeneity: Chi^2 = 1.69, df = 4 (P = 0.79); I^2 =0.0%

Test for overall effect: Z = 2.06 (P = 0.039)

Analysis 5.6. Comparison 5 Vaginal misoprostol versus PGF2alpha, Outcome 6 Side effects - any.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 5 Vaginal misoprostol versus PGF2alpha

Outcome: 6 Side effects - any

Study or subgroup	Vaginal Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Munthali 2001	7/30	7/31		100.0 %	1.03 [0.41, 2.59]
Total (95% CI)	**30**	**31**		**100.0 %**	**1.03 [0.41, 2.59]**

Total events: 7 (Vaginal Misoprostol), 7 (PGF2alpha)

Heterogeneity: not applicable

Test for overall effect: Z = 0.07 (P = 0.94)

Analysis 5.7. Comparison 5 Vaginal misoprostol versus PGF2alpha, Outcome 7 Nausea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 5 Vaginal misoprostol versus PGF2alpha

Outcome: 7 Nausea

Study or subgroup	Vaginal Misoprostol n/N	PGF2alphs n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	18/84	29/81		53.3 %	0.60 [0.36, 0.99]
Perry 1999	8/25	9/26		15.9 %	0.92 [0.42, 2.01]
Su 2005	11/61	17/61		30.7 %	0.65 [0.33, 1.26]
Total (95% CI)	**170**	**168**		**100.0 %**	**0.67 [0.47, 0.95]**
Total events: 37 (Vaginal Misoprostol), 55 (PGF2alphs)					
Heterogeneity: Chi^2 = 0.86, df = 2 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 2.24 (P = 0.025)					

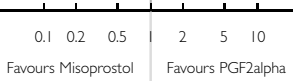
Analysis 5.8. Comparison 5 Vaginal misoprostol versus PGF2alpha, Outcome 8 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 5 Vaginal misoprostol versus PGF2alpha

Outcome: 8 Vomiting

Study or subgroup	Vaginal Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	22/84	31/81		55.8 %	0.68 [0.43, 1.08]
Ghorab 1998	1/20	9/20		15.9 %	0.11 [0.02, 0.80]
Perry 1999	3/25	2/26		3.5 %	1.56 [0.28, 8.56]
Su 2005	9/61	14/61		24.8 %	0.64 [0.30, 1.37]
Total (95% CI)	**190**	**188**		**100.0 %**	**0.61 [0.42, 0.89]**
Total events: 35 (Vaginal Misoprostol), 56 (PGF2alpha)					
Heterogeneity: Chi^2 = 4.28, df = 3 (P = 0.23); I^2 =30%					
Test for overall effect: Z = 2.61 (P = 0.00911)					



Analysis 5.9. Comparison 5 Vaginal misoprostol versus PGF2alpha, Outcome 9 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 5 Vaginal misoprostol versus PGF2alpha

Outcome: 9 Diarrhoea

Study or subgroup	Vaginal Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Akoury 2004	11/84	3/81		24.7 %	3.54 [1.02, 12.21]
Ghorab 1998	1/20	5/20		17.4 %	0.20 [0.03, 1.56]
Perry 1999	1/25	2/26		15.4 %	0.52 [0.05, 5.38]
Su 2005	11/61	20/61		29.9 %	0.55 [0.29, 1.05]
Zuo 1998	0/40	13/40		12.6 %	0.04 [0.00, 0.60]
Total (95% CI)	**230**	**228**		**100.0 %**	**0.52 [0.15, 1.82]**

Total events: 24 (Vaginal Misoprostol), 43 (PGF2alpha)

Heterogeneity: $Tau^2 = 1.28$; $Chi^2 = 13.11$, df = 4 (P = 0.01); $I^2 = 69\%$

Test for overall effect: Z = 1.03 (P = 0.30)

Analysis 5.10. Comparison 5 Vaginal misoprostol versus PGF2alpha, Outcome 10 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 5 Vaginal misoprostol versus PGF2alpha

Outcome: 10 Pyrexia

Study or subgroup	Vaginal Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Akoury 2004	9/84	11/81		23.7 %	0.79 [0.35, 1.80]
Ghorab 1998	2/20	14/20		21.5 %	0.14 [0.04, 0.55]
Perry 1999	2/25	1/26		16.5 %	2.08 [0.20, 21.52]
Su 2005	36/61	6/61		23.9 %	6.00 [2.73, 13.19]
Zuo 1998	0/40	8/40		14.3 %	0.06 [0.00, 0.99]
Total (95% CI)	**230**	**228**		**100.0 %**	**0.72 [0.14, 3.61]**

Total events: 49 (Vaginal Misoprostol), 40 (PGF2alpha)

Heterogeneity: $Tau^2 = 2.68$; $Chi^2 = 31.18$, df = 4 (P<0.00001); $I^2 = 87\%$

Test for overall effect: Z = 0.40 (P = 0.69)

Analysis 6.1. Comparison 6 Vaginal misoprostol versus vaginal misoprostol and oxytocin, Outcome 1 Mean induction to birth interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 6 Vaginal misoprostol versus vaginal misoprostol and oxytocin

Outcome: 1 Mean induction to birth interval

Study or subgroup	Vaginal Misoprostol N	Mean(SD)	PV misoprostol + oxy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Hidar 2001	35	27 (14.1)	41	22 (10.8)		100.0 %	5.00 [-0.72, 10.72]
Total (95% CI)	**35**		**41**			**100.0 %**	**5.00 [-0.72, 10.72]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.71 (P = 0.087)

Analysis 6.2. Comparison 6 Vaginal misoprostol versus vaginal misoprostol and oxytocin, Outcome 2 Surgical evacuation of the uterus.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 6 Vaginal misoprostol versus vaginal misoprostol and oxytocin

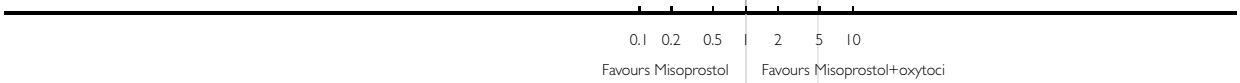
Outcome: 2 Surgical evacuation of the uterus

Study or subgroup	Vaginal Misoprostol n/N	PV misoprostol + oxy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hidar 2001	15/35	9/41		100.0 %	1.95 [0.98, 3.90]
Total (95% CI)	**35**	**41**		**100.0 %**	**1.95 [0.98, 3.90]**

Total events: 15 (Vaginal Misoprostol), 9 (PV misoprostol + oxy)

Heterogeneity: not applicable

Test for overall effect: Z = 1.89 (P = 0.058)



Analysis 6.4. Comparison 6 Vaginal misoprostol versus vaginal misoprostol and oxytocin, Outcome 4 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 6 Vaginal misoprostol versus vaginal misoprostol and oxytocin

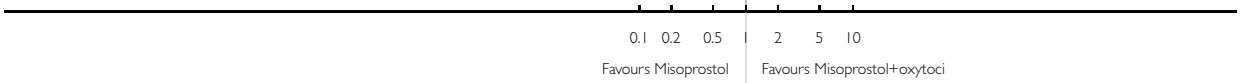
Outcome: 4 Vomiting

Study or subgroup	Vaginal Misoprostol n/N	PV misoprostol + oxy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hidar 2001	7/35	10/41		100.0 %	0.82 [0.35, 1.93]
Total (95% CI)	**35**	**41**		**100.0 %**	**0.82 [0.35, 1.93]**

Total events: 7 (Vaginal Misoprostol), 10 (PV misoprostol + oxy)

Heterogeneity: not applicable

Test for overall effect: Z = 0.46 (P = 0.65)



Analysis 6.5. Comparison 6 Vaginal misoprostol versus vaginal misoprostol and oxytocin, Outcome 5 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 6 Vaginal misoprostol versus vaginal misoprostol and oxytocin

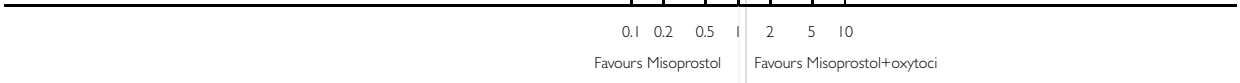
Outcome: 5 Diarrhoea

Study or subgroup	Vaginal Misoprostol n/N	PV misoprostol + oxy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hidar 2001	1/35	1/41		100.0 %	1.17 [0.08, 18.05]
Total (95% CI)	**35**	**41**		**100.0 %**	**1.17 [0.08, 18.05]**

Total events: 1 (Vaginal Misoprostol), 1 (PV misoprostol + oxy)

Heterogeneity: not applicable

Test for overall effect: Z = 0.11 (P = 0.91)



Analysis 6.6. Comparison 6 Vaginal misoprostol versus vaginal misoprostol and oxytocin, Outcome 6 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 6 Vaginal misoprostol versus vaginal misoprostol and oxytocin

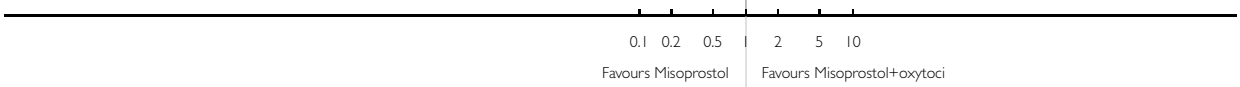
Outcome: 6 Pyrexia

Study or subgroup	Vaginal Misoprostol n/N	PV misoprostol + oxy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hidar 2001	8/35	4/41		100.0 %	2.34 [0.77, 7.13]
Total (95% CI)	**35**	**41**		**100.0 %**	**2.34 [0.77, 7.13]**

Total events: 8 (Vaginal Misoprostol), 4 (PV misoprostol + oxy)

Heterogeneity: not applicable

Test for overall effect: Z = 1.50 (P = 0.13)



Analysis 7.2. Comparison 7 Vaginal misoprostol versus glyceryl tri-nitrate, Outcome 2 Need for analgesia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 7 Vaginal misoprostol versus glyceryl tri-nitrate

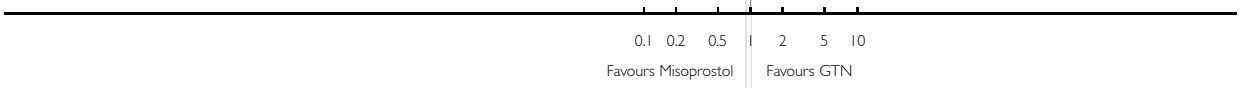
Outcome: 2 Need for analgesia

Study or subgroup	Vaginal Misoprostol n/N	PV misoprostol + GTN n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Makhlouf 2003	20/50	9/50		100.0 %	2.22 [1.12, 4.40]
Total (95% CI)	**50**	**50**		**100.0 %**	**2.22 [1.12, 4.40]**

Total events: 20 (Vaginal Misoprostol), 9 (PV misoprostol + GTN)

Heterogeneity: not applicable

Test for overall effect: Z = 2.29 (P = 0.022)



Analysis 7.3. Comparison 7 Vaginal misoprostol versus glyceryl tri-nitrate, Outcome 3 Blood loss > 500 mL.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 7 Vaginal misoprostol versus glyceryl tri-nitrate

Outcome: 3 Blood loss > 500 mL

Study or subgroup	Vaginal Misoprostol n/N	PV misoprostol + GTN n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Makhlouf 2003	7/50	0/50		100.0 %	15.00 [0.88, 255.78]
Total (95% CI)	**50**	**50**		**100.0 %**	**15.00 [0.88, 255.78]**
Total events: 7 (Vaginal Misoprostol), 0 (PV misoprostol + GTN)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.87 (P = 0.061)					

Analysis 7.4. Comparison 7 Vaginal misoprostol versus glyceryl tri-nitrate, Outcome 4 Surgical evacuation of the uterus.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 7 Vaginal misoprostol versus glyceryl tri-nitrate

Outcome: 4 Surgical evacuation of the uterus

Study or subgroup	Vaginal Misoprostol n/N	PV misoprostol + GTN n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Makhlouf 2003	4/50	0/50		100.0 %	9.00 [0.50, 162.89]
Total (95% CI)	**50**	**50**		**100.0 %**	**9.00 [0.50, 162.89]**
Total events: 4 (Vaginal Misoprostol), 0 (PV misoprostol + GTN)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.49 (P = 0.14)					

Analysis 7.5. Comparison 7 Vaginal misoprostol versus glyceryl tri-nitrate, Outcome 5 Side effects - any.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 7 Vaginal misoprostol versus glyceryl tri-nitrate

Outcome: 5 Side effects - any

Study or subgroup	Vaginal Misoprostol n/N	PV misoprostol + GTN n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Makhlouf 2003	37/50	0/50		100.0 %	75.00 [4.73, 1188.67]
Total (95% CI)	**50**	**50**		**100.0 %**	**75.00 [4.73, 1188.67]**
Total events: 37 (Vaginal Misoprostol), 0 (PV misoprostol + GTN)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.06 (P = 0.0022)					

Analysis 7.6. Comparison 7 Vaginal misoprostol versus glyceryl tri-nitrate, Outcome 6 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 7 Vaginal misoprostol versus glyceryl tri-nitrate

Outcome: 6 Vomiting

Study or subgroup	Vaginal Misoprostol n/N	PV misoprostol + GTN n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Makhlouf 2003	17/50	0/50		100.0 %	35.00 [2.16, 566.54]
Total (95% CI)	**50**	**50**		**100.0 %**	**35.00 [2.16, 566.54]**
Total events: 17 (Vaginal Misoprostol), 0 (PV misoprostol + GTN)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.50 (P = 0.012)					

Analysis 7.7. Comparison 7 Vaginal misoprostol versus glyceryl tri-nitrate, Outcome 7 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 7 Vaginal misoprostol versus glyceryl tri-nitrate

Outcome: 7 Diarrhoea

Study or subgroup	Vaginal Misoprostol n/N	PV misoprostol + GTN n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Makhlouf 2003	1/50	0/50		100.0 %	3.00 [0.13, 71.92]
Total (95% CI)	**50**	**50**		**100.0 %**	**3.00 [0.13, 71.92]**

Total events: 1 (Vaginal Misoprostol), 0 (PV misoprostol + GTN)

Heterogeneity: not applicable

Test for overall effect: Z = 0.68 (P = 0.50)

Analysis 7.8. Comparison 7 Vaginal misoprostol versus glyceryl tri-nitrate, Outcome 8 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 7 Vaginal misoprostol versus glyceryl tri-nitrate

Outcome: 8 Pyrexia

Study or subgroup	Vaginal Misoprostol n/N	PV misoprostol + GTN n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Makhlouf 2003	15/50	0/50		100.0 %	31.00 [1.91, 504.35]
Total (95% CI)	**50**	**50**		**100.0 %**	**31.00 [1.91, 504.35]**

Total events: 15 (Vaginal Misoprostol), 0 (PV misoprostol + GTN)

Heterogeneity: not applicable

Test for overall effect: Z = 2.41 (P = 0.016)

Analysis 8.1. Comparison 8 Vaginal misoprostol versus vaginal misoprostol and laminaria, Outcome 1 Vaginal birth not achieved in 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 8 Vaginal misoprostol versus vaginal misoprostol and laminaria

Outcome: 1 Vaginal birth not achieved in 24 hours

Study or subgroup	Vaginal Misoprostol n/N	PV misopr./laminaria n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jain 1994	10/33	11/35		100.0 %	0.96 [0.47, 1.97]
Total (95% CI)	**33**	**35**		**100.0 %**	**0.96 [0.47, 1.97]**
Total events: 10 (Vaginal Misoprostol), 11 (PV misopr./laminaria)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.10 (P = 0.92)					

Analysis 8.2. Comparison 8 Vaginal misoprostol versus vaginal misoprostol and laminaria, Outcome 2 Blood loss > 500 mL.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 8 Vaginal misoprostol versus vaginal misoprostol and laminaria

Outcome: 2 Blood loss > 500 mL

Study or subgroup	Vaginal Misoprostol n/N	PV misopr./laminaria n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Jain 1994	0/33	0/35		0.0 [0.0, 0.0]
Total (95% CI)	**33**	**35**		**0.0 [0.0, 0.0]**
Total events: 0 (Vaginal Misoprostol), 0 (PV misopr./laminaria)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 8.3. Comparison 8 Vaginal misoprostol versus vaginal misoprostol and laminaria, Outcome 3 Need for blood transfusion.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 8 Vaginal misoprostol versus vaginal misoprostol and laminaria

Outcome: 3 Need for blood transfusion

Study or subgroup	Vaginal Misoprostol n/N	PV misopr./laminaria n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Jain 1994	0/33	0/35		0.0 [0.0, 0.0]
Total (95% CI)	**33**	**35**		**0.0 [0.0, 0.0]**
Total events: 0 (Vaginal Misoprostol), 0 (PV misopr./laminaria)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 8.4. Comparison 8 Vaginal misoprostol versus vaginal misoprostol and laminaria, Outcome 4 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 8 Vaginal misoprostol versus vaginal misoprostol and laminaria

Outcome: 4 Vomiting

Study or subgroup	Vaginal Misoprostol n/N	PV misopr./laminaria n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jain 1994	2/33	3/35		100.0 %	0.71 [0.13, 3.97]
Total (95% CI)	**33**	**35**		**100.0 %**	**0.71 [0.13, 3.97]**
Total events: 2 (Vaginal Misoprostol), 3 (PV misopr./laminaria)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.39 (P = 0.69)					

Analysis 8.5. Comparison 8 Vaginal misoprostol versus vaginal misoprostol and laminaria, Outcome 5 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 8 Vaginal misoprostol versus vaginal misoprostol and laminaria

Outcome: 5 Diarrhoea

Study or subgroup	Vaginal Misoprostol n/N	PV misopr./laminaria n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jain 1994	0/33	1/35		100.0 %	0.35 [0.01, 8.37]
Total (95% CI)	**33**	**35**		**100.0 %**	**0.35 [0.01, 8.37]**

Total events: 0 (Vaginal Misoprostol), 1 (PV misopr./laminaria)

Heterogeneity: not applicable

Test for overall effect: Z = 0.64 (P = 0.52)

Analysis 8.6. Comparison 8 Vaginal misoprostol versus vaginal misoprostol and laminaria, Outcome 6 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 8 Vaginal misoprostol versus vaginal misoprostol and laminaria

Outcome: 6 Pyrexia

Study or subgroup	Vaginal Misoprostol n/N	PV misopr./laminaria n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jain 1994	1/33	5/35		100.0 %	0.21 [0.03, 1.72]
Total (95% CI)	**33**	**35**		**100.0 %**	**0.21 [0.03, 1.72]**

Total events: 1 (Vaginal Misoprostol), 5 (PV misopr./laminaria)

Heterogeneity: not applicable

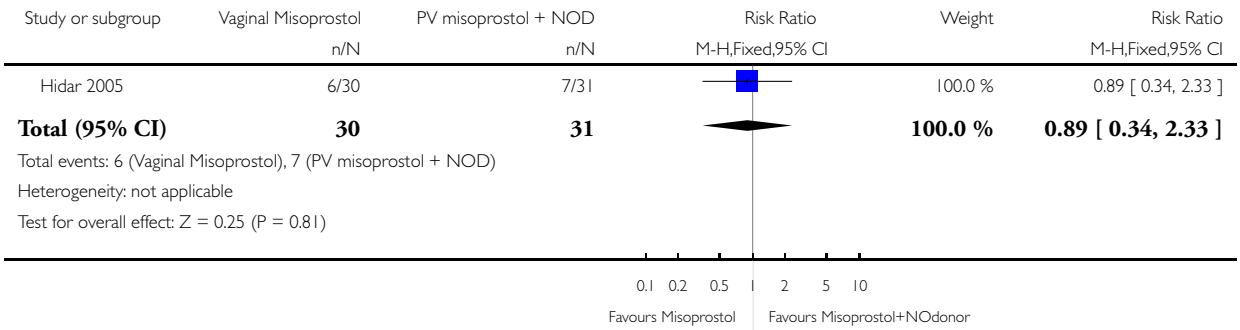
Test for overall effect: Z = 1.45 (P = 0.15)

Analysis 9.1. Comparison 9 Vaginal misoprostol versus vaginal misoprostol and nitric oxide donor, Outcome 1 Vaginal birth not achieved in 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 9 Vaginal misoprostol versus vaginal misoprostol and nitric oxide donor

Outcome: 1 Vaginal birth not achieved in 24 hours

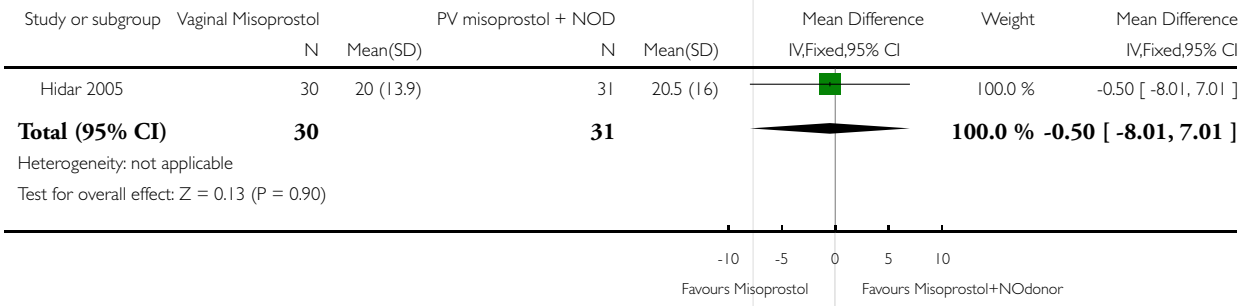


Analysis 9.2. Comparison 9 Vaginal misoprostol versus vaginal misoprostol and nitric oxide donor, Outcome 2 Mean induction to birth interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 9 Vaginal misoprostol versus vaginal misoprostol and nitric oxide donor

Outcome: 2 Mean induction to birth interval

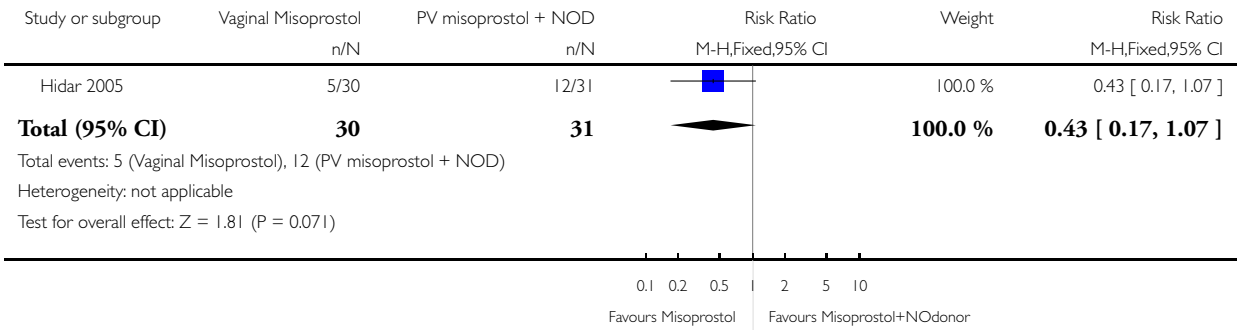


Analysis 9.3. Comparison 9 Vaginal misoprostol versus vaginal misoprostol and nitric oxide donor, Outcome 3 Side effects - any.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 9 Vaginal misoprostol versus vaginal misoprostol and nitric oxide donor

Outcome: 3 Side effects - any

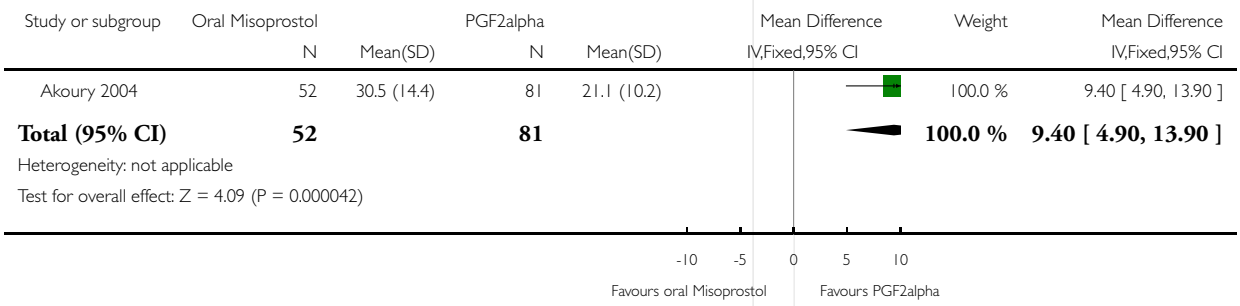


Analysis 10.1. Comparison 10 Oral misoprostol versus PGF2alpha, Outcome 1 Mean induction to birth interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 10 Oral misoprostol versus PGF2alpha

Outcome: 1 Mean induction to birth interval



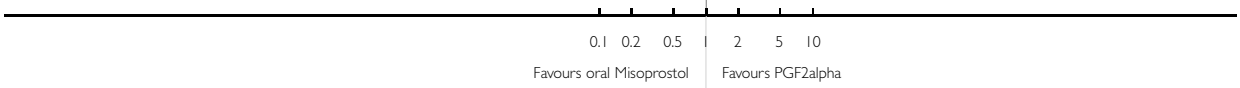
Analysis 10.2. Comparison 10 Oral misoprostol versus PGF2alpha, Outcome 2 Surgical evacuation of the uterus.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 10 Oral misoprostol versus PGF2alpha

Outcome: 2 Surgical evacuation of the uterus

Study or subgroup	Oral Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	8/52	16/81		100.0 %	0.78 [0.36, 1.69]
Total (95% CI)	**52**	**81**		**100.0 %**	**0.78 [0.36, 1.69]**
Total events: 8 (Oral Misoprostol), 16 (PGF2alpha)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					



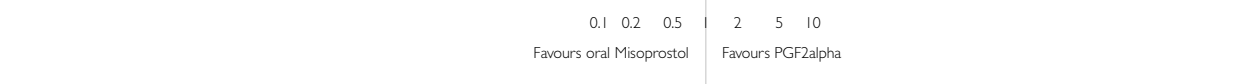
Analysis 10.3. Comparison 10 Oral misoprostol versus PGF2alpha, Outcome 3 Nausea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 10 Oral misoprostol versus PGF2alpha

Outcome: 3 Nausea

Study or subgroup	Oral Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	17/52	29/81		100.0 %	0.91 [0.56, 1.49]
Total (95% CI)	**52**	**81**		**100.0 %**	**0.91 [0.56, 1.49]**
Total events: 17 (Oral Misoprostol), 29 (PGF2alpha)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					



Analysis 10.4. Comparison 10 Oral misoprostol versus PGF2alpha, Outcome 4 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 10 Oral misoprostol versus PGF2alpha

Outcome: 4 Vomiting

Study or subgroup	Oral Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	17/52	29/81		100.0 %	0.91 [0.56, 1.49]
Total (95% CI)	**52**	**81**		**100.0 %**	**0.91 [0.56, 1.49]**
Total events: 17 (Oral Misoprostol), 29 (PGF2alpha)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					

Analysis 10.5. Comparison 10 Oral misoprostol versus PGF2alpha, Outcome 5 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 10 Oral misoprostol versus PGF2alpha

Outcome: 5 Diarrhoea

Study or subgroup	Oral Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	5/52	3/81		100.0 %	2.60 [0.65, 10.41]
Total (95% CI)	**52**	**81**		**100.0 %**	**2.60 [0.65, 10.41]**
Total events: 5 (Oral Misoprostol), 3 (PGF2alpha)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.35 (P = 0.18)					

Analysis 10.6. Comparison 10 Oral misoprostol versus PGF2alpha, Outcome 6 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 10 Oral misoprostol versus PGF2alpha

Outcome: 6 Pyrexia

Study or subgroup	Oral Misoprostol n/N	PGF2alpha n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Akoury 2004	9/52	11/81		100.0 %	1.27 [0.57, 2.86]
Total (95% CI)	**52**	**81**		**100.0 %**	**1.27 [0.57, 2.86]**
Total events: 9 (Oral Misoprostol), 11 (PGF2alpha)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.56)					

Analysis 11.1. Comparison 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone, Outcome 1 Vaginal birth not achieved in 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone

Outcome: 1 Vaginal birth not achieved in 24 hours

Study or subgroup	PO/PV Misoprostol n/N	Vaginal Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	7/27	4/28		100.0 %	1.81 [0.60, 5.50]
Total (95% CI)	**27**	**28**		**100.0 %**	**1.81 [0.60, 5.50]**
Total events: 7 (PO/PV Misoprostol), 4 (Vaginal Misoprostol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					

Analysis 11.2. Comparison 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone, Outcome 2 Mean induction to birth interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone

Outcome: 2 Mean induction to birth interval

Study or subgroup	PO/PV Misoprostol N	Mean(SD)	Vaginal Misoprostol N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Feldman 2003	21	21.1 (3.5)	22	15.9 (2.3)		100.0 %	5.20 [3.42, 6.98]
Total (95% CI)	**21**		**22**			**100.0 %**	**5.20 [3.42, 6.98]**

Heterogeneity: not applicable

Test for overall effect: Z = 5.73 (P < 0.00001)

Analysis 11.3. Comparison 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone, Outcome 3 Need for analgesia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone

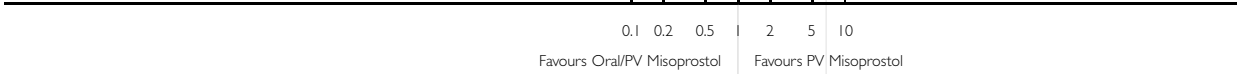
Outcome: 3 Need for analgesia

Study or subgroup	PO/PV Misoprostol n/N	Vaginal Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	21/27	21/28		100.0 %	1.04 [0.77, 1.39]
Total (95% CI)	**27**	**28**		**100.0 %**	**1.04 [0.77, 1.39]**

Total events: 21 (PO/PV Misoprostol), 21 (Vaginal Misoprostol)

Heterogeneity: not applicable

Test for overall effect: Z = 0.24 (P = 0.81)



Analysis 11.5. Comparison 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone, Outcome 5 Surgical evacuation of the uterus.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone

Outcome: 5 Surgical evacuation of the uterus

Study or subgroup	PO/PV Misoprostol n/N	Vaginal Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	8/27	12/28		80.1 %	0.69 [0.34, 1.42]
Feldman 2003	4/21	3/22		19.9 %	1.40 [0.35, 5.51]
Total (95% CI)	**48**	**50**		**100.0 %**	**0.83 [0.44, 1.57]**
Total events: 12 (PO/PV Misoprostol), 15 (Vaginal Misoprostol)					
Heterogeneity: Chi^2 = 0.80, df = 1 (P = 0.37); I^2 =0.0%					
Test for overall effect: Z = 0.57 (P = 0.57)					

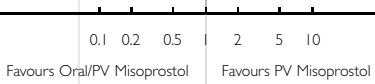
Analysis 11.6. Comparison 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone, Outcome 6 Nausea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone

Outcome: 6 Nausea

Study or subgroup	PO/PV Misoprostol n/N	Vaginal Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	0/27	0/28		0.0 [0.0, 0.0]
Total (95% CI)	**27**	**28**		**0.0 [0.0, 0.0]**
Total events: 0 (PO/PV Misoprostol), 0 (Vaginal Misoprostol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



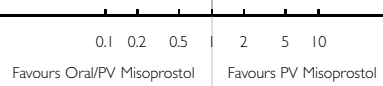
Analysis 11.7. Comparison 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone, Outcome 7 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone

Outcome: 7 Vomiting

Study or subgroup	PO/PV Misoprostol n/N	Vaginal Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	0/27	0/28		0.0 [0.0, 0.0]
Total (95% CI)	**27**	**28**		**0.0 [0.0, 0.0]**
Total events: 0 (PO/PV Misoprostol), 0 (Vaginal Misoprostol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



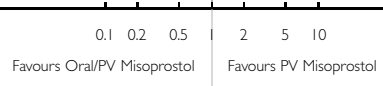
Analysis 11.8. Comparison 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone, Outcome 8 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 11 Combined oral and vaginal misoprostol versus vaginal misoprostol alone

Outcome: 8 Diarrhoea

Study or subgroup	PO/PV Misoprostol n/N	Vaginal Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	0/27	0/28		0.0 [0.0, 0.0]
Total (95% CI)	**27**	**28**		**0.0 [0.0, 0.0]**
Total events: 0 (PO/PV Misoprostol), 0 (Vaginal Misoprostol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



Analysis 12.1. Comparison 12 Combined oral and vaginal misoprostol versus oral misoprostol alone, Outcome 1 Vaginal birth not achieved in 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 12 Combined oral and vaginal misoprostol versus oral misoprostol alone

Outcome: 1 Vaginal birth not achieved in 24 hours

Study or subgroup	PO/PV Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	7/27	16/29		100.0 %	0.47 [0.23, 0.96]
Total (95% CI)	**27**	**29**		**100.0 %**	**0.47 [0.23, 0.96]**
Total events: 7 (PO/PV Misoprostol), 16 (Oral Misoprostol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.06 (P = 0.039)					

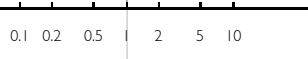
Analysis 12.2. Comparison 12 Combined oral and vaginal misoprostol versus oral misoprostol alone, Outcome 2 Need for analgesia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 12 Combined oral and vaginal misoprostol versus oral misoprostol alone

Outcome: 2 Need for analgesia

Study or subgroup	PO/PV Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	21/27	20/29		100.0 %	1.13 [0.82, 1.55]
Total (95% CI)	**27**	**29**		**100.0 %**	**1.13 [0.82, 1.55]**
Total events: 21 (PO/PV Misoprostol), 20 (Oral Misoprostol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.74 (P = 0.46)					



Analysis 12.3. Comparison 12 Combined oral and vaginal misoprostol versus oral misoprostol alone, Outcome 3 Surgical evacuation of the uterus.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 12 Combined oral and vaginal misoprostol versus oral misoprostol alone

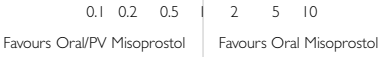
Outcome: 3 Surgical evacuation of the uterus

Study or subgroup	PO/PV Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	8/27	10/29		100.0 %	0.86 [0.40, 1.85]
Total (95% CI)	**27**	**29**		**100.0 %**	**0.86 [0.40, 1.85]**

Total events: 8 (PO/PV Misoprostol), 10 (Oral Misoprostol)

Heterogeneity: not applicable

Test for overall effect: Z = 0.39 (P = 0.70)



Analysis 12.4. Comparison 12 Combined oral and vaginal misoprostol versus oral misoprostol alone, Outcome 4 Nausea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 12 Combined oral and vaginal misoprostol versus oral misoprostol alone

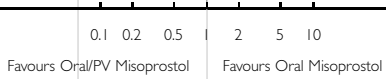
Outcome: 4 Nausea

Study or subgroup	PO/PV Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	0/27	0/29		0.0 [0.0, 0.0]
Total (95% CI)	**27**	**29**		**0.0 [0.0, 0.0]**

Total events: 0 (PO/PV Misoprostol), 0 (Oral Misoprostol)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)



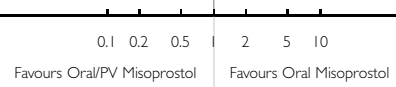
Analysis 12.5. Comparison 12 Combined oral and vaginal misoprostol versus oral misoprostol alone, Outcome 5 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 12 Combined oral and vaginal misoprostol versus oral misoprostol alone

Outcome: 5 Vomiting

Study or subgroup	PO/PV Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	0/27	0/29		0.0 [0.0, 0.0]
Total (95% CI)	**27**	**29**		**0.0 [0.0, 0.0]**
Total events: 0 (PO/PV Misoprostol), 0 (Oral Misoprostol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



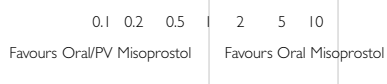
Analysis 12.6. Comparison 12 Combined oral and vaginal misoprostol versus oral misoprostol alone, Outcome 6 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 12 Combined oral and vaginal misoprostol versus oral misoprostol alone

Outcome: 6 Diarrhoea

Study or subgroup	PO/PV Misoprostol n/N	Oral Misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2003	0/27	3/29		100.0 %	0.15 [0.01, 2.83]
Total (95% CI)	**27**	**29**		**100.0 %**	**0.15 [0.01, 2.83]**
Total events: 0 (PO/PV Misoprostol), 3 (Oral Misoprostol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.26 (P = 0.21)					



Analysis 13.1. Comparison 13 Combined oral and vaginal misoprostol versus dilation and evacuation, Outcome 1 Nausea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 13 Combined oral and vaginal misoprostol versus dilation and evacuation

Outcome: 1 Nausea

Study or subgroup	PO/PV Misoprostol n/N	Dilation/Evacuation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grimes 2005	5/9	3/9		100.0 %	1.67 [0.56, 4.97]
Total (95% CI)	**9**	**9**		**100.0 %**	**1.67 [0.56, 4.97]**
Total events: 5 (PO/PV Misoprostol), 3 (Dilation/Evacuation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					

Analysis 13.2. Comparison 13 Combined oral and vaginal misoprostol versus dilation and evacuation, Outcome 2 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 13 Combined oral and vaginal misoprostol versus dilation and evacuation

Outcome: 2 Vomiting

Study or subgroup	PO/PV Misoprostol n/N	Dilation/Evacuation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grimes 2005	4/9	2/9		100.0 %	2.00 [0.48, 8.31]
Total (95% CI)	**9**	**9**		**100.0 %**	**2.00 [0.48, 8.31]**
Total events: 4 (PO/PV Misoprostol), 2 (Dilation/Evacuation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					

Analysis 13.3. Comparison 13 Combined oral and vaginal misoprostol versus dilation and evacuation, Outcome 3 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 13 Combined oral and vaginal misoprostol versus dilation and evacuation

Outcome: 3 Diarrhoea

Study or subgroup	PO/PV Misoprostol n/N	Dilation/Evacuation n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Grimes 2005	0/9	0/9		0.0 [0.0, 0.0]
Total (95% CI)	**9**	**9**		**0.0 [0.0, 0.0]**
Total events: 0 (PO/PV Misoprostol), 0 (Dilation/Evacuation)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 14.1. Comparison 14 Sublingual misoprostol versus vaginal misoprostol, Outcome 1 Vaginal birth not achieved in 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 14 Sublingual misoprostol versus vaginal misoprostol

Outcome: 1 Vaginal birth not achieved in 24 hours

Study or subgroup	Sublingual misoprostol n/N	Vaginal misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2005	3/51	12/51		82.8 %	0.25 [0.07, 0.83]
Elhassan 2008	0/50	2/50		17.2 %	0.20 [0.01, 4.06]
Total (95% CI)	**101**	**101**		**100.0 %**	**0.24 [0.08, 0.74]**
Total events: 3 (Sublingual misoprostol), 14 (Vaginal misoprostol)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 2.49 (P = 0.013)					

Analysis 14.2. Comparison 14 Sublingual misoprostol versus vaginal misoprostol, Outcome 2 Induction to delivery interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 14 Sublingual misoprostol versus vaginal misoprostol

Outcome: 2 Induction to delivery interval

Study or subgroup	Sublingual misoprostol N	Mean(SD)	Vaginal misoprostol N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Caliskan 2005	51	10.8 (8.4)	51	17.8 (10.6)		39.2 %	-7.00 [-10.71, -3.29]
Elhassan 2008	50	10.5 (3.7)	50	13.9 (5.1)		60.8 %	-3.40 [-5.15, -1.65]
Total (95% CI)	**101**		**101**			**100.0 %**	**-4.81 [-8.26, -1.37]**

Heterogeneity: $Tau^2 = 4.29$; $Chi^2 = 2.96$, df = 1 (P = 0.09); $I^2 = 66\%$

Test for overall effect: Z = 2.74 (P = 0.0062)

Analysis 14.3. Comparison 14 Sublingual misoprostol versus vaginal misoprostol, Outcome 3 Analgesic requirements.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 14 Sublingual misoprostol versus vaginal misoprostol

Outcome: 3 Analgesic requirements

Study or subgroup	Sublingual misoprostol n/N	Vaginal misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2005	9/51	9/51		100.0 %	1.00 [0.43, 2.31]
Total (95% CI)	**51**	**51**		**100.0 %**	**1.00 [0.43, 2.31]**

Total events: 9 (Sublingual misoprostol), 9 (Vaginal misoprostol)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Analysis 14.4. Comparison 14 Sublingual misoprostol versus vaginal misoprostol, Outcome 4 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 14 Sublingual misoprostol versus vaginal misoprostol

Outcome: 4 Vomiting

Study or subgroup	Sublingual misoprostol n/N	Vaginal misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2005	11/51	16/51		100.0 %	0.69 [0.35, 1.33]
Total (95% CI)	**51**	**51**		**100.0 %**	**0.69 [0.35, 1.33]**

Total events: 11 (Sublingual misoprostol), 16 (Vaginal misoprostol)

Heterogeneity: not applicable

Test for overall effect: Z = 1.11 (P = 0.27)

Analysis 14.5. Comparison 14 Sublingual misoprostol versus vaginal misoprostol, Outcome 5 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 14 Sublingual misoprostol versus vaginal misoprostol

Outcome: 5 Diarrhoea

Study or subgroup	Sublingual misoprostol n/N	Vaginal misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2005	5/51	2/51		100.0 %	2.50 [0.51, 12.30]
Total (95% CI)	**51**	**51**		**100.0 %**	**2.50 [0.51, 12.30]**

Total events: 5 (Sublingual misoprostol), 2 (Vaginal misoprostol)

Heterogeneity: not applicable

Test for overall effect: Z = 1.13 (P = 0.26)

Analysis 14.6. Comparison 14 Sublingual misoprostol versus vaginal misoprostol, Outcome 6 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 14 Sublingual misoprostol versus vaginal misoprostol

Outcome: 6 Pyrexia

Study or subgroup	Sublingual misoprostol n/N	Vaginal misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2005	6/51	6/51		100.0 %	1.00 [0.35, 2.89]
Total (95% CI)	**51**	**51**		**100.0 %**	**1.00 [0.35, 2.89]**

Total events: 6 (Sublingual misoprostol), 6 (Vaginal misoprostol)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Analysis 15.1. Comparison 15 Sublingual misoprostol versus oral misoprostol, Outcome 1 Vaginal birth not achieved within 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 15 Sublingual misoprostol versus oral misoprostol

Outcome: 1 Vaginal birth not achieved within 24 hours

Study or subgroup	Sublingual misoprostol n/N	Oral misoprostol n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Caliskan 2005	3/51	4/51		57.3 %	0.75 [0.18, 3.18]
Elhassan 2008	0/51	11/51		42.7 %	0.04 [0.00, 0.72]
Total (95% CI)	**102**	**102**		**100.0 %**	**0.22 [0.01, 4.99]**

Total events: 3 (Sublingual misoprostol), 15 (Oral misoprostol)

Heterogeneity: $Tau^2 = 3.85$; $Chi^2 = 3.97$, df = 1 (P = 0.05); $I^2 = 75\%$

Test for overall effect: Z = 0.95 (P = 0.34)

Analysis 15.2. Comparison 15 Sublingual misoprostol versus oral misoprostol, Outcome 2 Induction to delivery interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 15 Sublingual misoprostol versus oral misoprostol

Outcome: 2 Induction to delivery interval

Study or subgroup	Sublingual misoprostol N	Mean(SD)	Oral misoprostol N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Caliskan 2005	51	10.8 (8.4)	51	14.6 (8.3)		49.7 %	-3.80 [-7.04, -0.56]
Elhassan 2008	50	10.5 (3.7)	50	21 (10.5)		50.3 %	-10.50 [-13.59, -7.41]
Total (95% CI)	**101**		**101**			**100.0 %**	**-7.17 [-13.73, -0.60]**

Heterogeneity: Tau^2 = 19.84; Chi^2 = 8.61, df = 1 (P = 0.003); I^2 =88%

Test for overall effect: Z = 2.14 (P = 0.032)

Analysis 15.3. Comparison 15 Sublingual misoprostol versus oral misoprostol, Outcome 3 Analgesic requirements.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 15 Sublingual misoprostol versus oral misoprostol

Outcome: 3 Analgesic requirements

Study or subgroup	Sublingual misoprostol n/N	Oral misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2005	9/51	14/51		100.0 %	0.64 [0.31, 1.35]
Total (95% CI)	**51**	**51**		**100.0 %**	**0.64 [0.31, 1.35]**

Total events: 9 (Sublingual misoprostol), 14 (Oral misoprostol)

Heterogeneity: not applicable

Test for overall effect: Z = 1.17 (P = 0.24)

Analysis 15.4. Comparison 15 Sublingual misoprostol versus oral misoprostol, Outcome 4 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 15 Sublingual misoprostol versus oral misoprostol

Outcome: 4 Vomiting

Study or subgroup	Sublingual misoprostol n/N	Oral misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2005	11/51	13/51		100.0 %	0.85 [0.42, 1.71]
Total (95% CI)	**51**	**51**		**100.0 %**	**0.85 [0.42, 1.71]**
Total events: 11 (Sublingual misoprostol), 13 (Oral misoprostol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.47 (P = 0.64)					

Analysis 15.5. Comparison 15 Sublingual misoprostol versus oral misoprostol, Outcome 5 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 15 Sublingual misoprostol versus oral misoprostol

Outcome: 5 Diarrhoea

Study or subgroup	Sublingual misoprostol n/N	Oral misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2005	5/51	6/51		100.0 %	0.83 [0.27, 2.56]
Total (95% CI)	**51**	**51**		**100.0 %**	**0.83 [0.27, 2.56]**
Total events: 5 (Sublingual misoprostol), 6 (Oral misoprostol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					

Analysis 15.6. Comparison 15 Sublingual misoprostol versus oral misoprostol, Outcome 6 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 15 Sublingual misoprostol versus oral misoprostol

Outcome: 6 Pyrexia

Study or subgroup	Sublingual misoprostol n/N	Oral misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2005	6/51	10/51		100.0 %	0.60 [0.24, 1.53]
Total (95% CI)	**51**	**51**		**100.0 %**	**0.60 [0.24, 1.53]**
Total events: 6 (Sublingual misoprostol), 10 (Oral misoprostol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.28)					

Analysis 16.1. Comparison 16 Sublingual misoprostol 100 mcg versus sublingual misoprostol 200 mcg, Outcome 1 Induction to delivery interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 16 Sublingual misoprostol 100 mcg versus sublingual misoprostol 200 mcg

Outcome: 1 Induction to delivery interval

Study or subgroup	100mcg misoprostol N	Mean(SD)	200mcg misoprostol N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Caliskan 2009	81	14.8 (8.7)	81	15.27 (7.25)		100.0 %	-0.47 [-2.94, 2.00]
Total (95% CI)	**81**		**81**			**100.0 %**	**-0.47 [-2.94, 2.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.37 (P = 0.71)							

Analysis 16.2. Comparison 16 Sublingual misoprostol 100 mcg versus sublingual misoprostol 200 mcg, Outcome 2 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 16 Sublingual misoprostol 100 mcg versus sublingual misoprostol 200 mcg

Outcome: 2 Vomiting

Study or subgroup	100mcg misoprostol n/N	200mcg misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2009	7/81	13/81		100.0 %	0.54 [0.23, 1.28]
Total (95% CI)	**81**	**81**		**100.0 %**	**0.54 [0.23, 1.28]**
Total events: 7 (100mcg misoprostol), 13 (200mcg misoprostol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.40 (P = 0.16)					

Analysis 16.3. Comparison 16 Sublingual misoprostol 100 mcg versus sublingual misoprostol 200 mcg, Outcome 3 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 16 Sublingual misoprostol 100 mcg versus sublingual misoprostol 200 mcg

Outcome: 3 Diarrhoea

Study or subgroup	100mcg misoprostol n/N	200mcg misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2009	5/81	8/81		100.0 %	0.63 [0.21, 1.83]
Total (95% CI)	**81**	**81**		**100.0 %**	**0.63 [0.21, 1.83]**
Total events: 5 (100mcg misoprostol), 8 (200mcg misoprostol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.86 (P = 0.39)					

Analysis 16.4. Comparison 16 Sublingual misoprostol 100 mcg versus sublingual misoprostol 200 mcg, Outcome 4 Pyrexia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 16 Sublingual misoprostol 100 mcg versus sublingual misoprostol 200 mcg

Outcome: 4 Pyrexia

Study or subgroup	100mcg misoprostol n/N	200mcg misoprostol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caliskan 2009	11/81	17/81		100.0 %	0.65 [0.32, 1.29]
Total (95% CI)	**81**	**81**		**100.0 %**	**0.65 [0.32, 1.29]**
Total events: 11 (100mcg misoprostol), 17 (200mcg misoprostol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.23 (P = 0.22)					

Analysis 17.1. Comparison 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose), Outcome 1 Vaginal birth not achieved in 24 hours.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose)

Outcome: 1 Vaginal birth not achieved in 24 hours

Study or subgroup	Low n/N	Moderate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2002	21/51	22/99		100.0 %	1.85 [1.13, 3.03]
Total (95% CI)	**51**	**99**		**100.0 %**	**1.85 [1.13, 3.03]**
Total events: 21 (Low), 22 (Moderate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.45 (P = 0.014)					

Analysis 17.2. Comparison 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose), Outcome 2 Pain (VAS score > 5).

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose)

Outcome: 2 Pain (VAS score > 5)

Study or subgroup	Low n/N	Moderate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2002	11/51	24/99		100.0 %	0.89 [0.47, 1.67]
Total (95% CI)	**51**	**99**		**100.0 %**	**0.89 [0.47, 1.67]**
Total events: 11 (Low), 24 (Moderate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					

Analysis 17.3. Comparison 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose), Outcome 3 Need for analgesia.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose)

Outcome: 3 Need for analgesia

Study or subgroup	Low n/N	Moderate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2002	36/51	78/99		100.0 %	0.90 [0.73, 1.10]
Total (95% CI)	**51**	**99**		**100.0 %**	**0.90 [0.73, 1.10]**
Total events: 36 (Low), 78 (Moderate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					

Analysis 17.4. Comparison 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose), Outcome 4 Surgical evacuation of the uterus.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose)

Outcome: 4 Surgical evacuation of the uterus

Study or subgroup	Low n/N	Moderate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2002	12/51	41/99		100.0 %	0.57 [0.33, 0.98]
Total (95% CI)	**51**	**99**		**100.0 %**	**0.57 [0.33, 0.98]**
Total events: 12 (Low), 41 (Moderate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.02 (P = 0.043)					

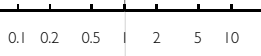
Analysis 17.5. Comparison 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose), Outcome 5 Nausea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose)

Outcome: 5 Nausea

Study or subgroup	Low n/N	Moderate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2002	16/51	32/99		100.0 %	0.97 [0.59, 1.59]
Total (95% CI)	**51**	**99**		**100.0 %**	**0.97 [0.59, 1.59]**
Total events: 16 (Low), 32 (Moderate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.91)					



Analysis 17.6. Comparison 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose), Outcome 6 Vomiting.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose)

Outcome: 6 Vomiting

Study or subgroup	Low n/N	Moderate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2002	8/51	27/99		100.0 %	0.58 [0.28, 1.17]
Total (95% CI)	**51**	**99**		**100.0 %**	**0.58 [0.28, 1.17]**
Total events: 8 (Low), 27 (Moderate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.52 (P = 0.13)					

Analysis 17.7. Comparison 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose), Outcome 7 Diarrhoea.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 17 Vaginal misoprostol - low (< 800 mcg cumulative dose) versus moderate (800 mcg -2400 mcg cumulative dose)

Outcome: 7 Diarrhoea

Study or subgroup	Low n/N	Moderate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dickinson 2002	7/51	6/99		100.0 %	2.26 [0.80, 6.39]
Total (95% CI)	**51**	**99**		**100.0 %**	**2.26 [0.80, 6.39]**
Total events: 7 (Low), 6 (Moderate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					

Analysis 18.1. Comparison 18 Vaginal misoprostol - moderate dose (cumulative dose 2400 mcg) versus high dose (cumulative dose 3200 mcg), Outcome 1 Mean induction to birth interval.

Review: Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

Comparison: 18 Vaginal misoprostol - moderate dose (cumulative dose 2400 mcg) versus high dose (cumulative dose 3200 mcg)

Outcome: 1 Mean induction to birth interval

Study or subgroup	Moderate N	Mean(SD)	High N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pongsatha 2004	88	19.9 (10.7)	90	15.7 (8.5)		100.0 %	4.20 [1.36, 7.04]
Total (95% CI)	**88**		**90**			**100.0 %**	**4.20 [1.36, 7.04]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.90 (P = 0.0038)

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 4, 2010

CONTRIBUTIONS OF AUTHORS

Jodie Dodd drafted the original protocol; both authors contributed to data extraction and interpretation of the findings, and were involved in all aspects of the development of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Discipline of Obstetrics and Gynaecology, University of Adelaide, Australia.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated our methods text to reflect the Cochrane Pregnancy and Childbirth Group's latest methods.

INDEX TERMS

Medical Subject Headings (MeSH)

*Abortifacient Agents, Nonsteroidal; *Misoprostol; *Oxytocics; Abortion, Induced [*methods]; Congenital Abnormalities; Fetal Death; Labor, Induced [*methods]; Pregnancy Trimester, Second; Pregnancy Trimester, Third; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy