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[Intervention Review]

Medical methods for mid-trimester termination of pregnancy

Hajo Wildschut[1], Marieke I Both[1], Suzanne Medema[2], Eeke Thomee[3], Mark F Wildhagen[4], Nathalie Kapp[5]

[1]Department of Obstetrics and Gynaecology, Erasmus Medical Center, Rotterdam, Netherlands. [2]Bouman GGZ, Rotterdam, Netherlands. [3]The Royal Marsden Hospital, London, UK. [4]Department of Urology and Obstetrics and Gynecology, Erasmus Medical Center, Rotterdam, Netherlands. [5]Department of Reproductive Health and Research, World Health Organization, Geneva 27, Switzerland

Contact: Hajo Wildschut, Department of Obstetrics and Gynaecology, Erasmus Medical Center, PO Box 2040, Rotterdam, 3000 CA, Netherlands. h.wildschut@erasmusmc.nl.

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ABSTRACT

Background

With the improvement of ultrasound technology, the likelihood of detection of major fetal structural anomalies in mid-pregnancy has increased considerably. Upon the detection of serious anomalies, women typically are offered the option of pregnancy termination. Additionally, there are still many reasons other than fetal anomalies why women seek abortion in the mid-trimester.

Objectives

To compare different methods of second trimester medical termination of pregnancy for their efficacy and side-effects.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE, Popline and reference lists of retrieved papers and other sources.

Selection criteria

All randomised controlled trials (RCTs) examining medical regimens for termination of pregnancy of a singleton living fetus between 12-28 weeks' gestation were analysed. The outcome measures were the induction to abortion interval, abortion rate within 24 hours, need for surgical evacuation, blood loss, uterine rupture, pain, and side-effects.Trials including >20% fetal death, multiple pregnancies, previous uterine scars and regimens which involved cervical preparation were excluded.

Data collection and analysis

Two authors selected the trials and three authors extracted data.

Main results

Fourty RCTs were included, addressing various agents for pregnancy termination and methods of administration. When used alone, misoprostol was an effective inductive agent, though it appeared to be more effective in combination with mifepristone. However, the evidence from RCTs is limited.

Misoprostol was preferably administered vaginally, although among multiparous women sublingual administration appeared equally effective. A range of doses of vaginally administered misoprostol has been used. No randomised trials comparing doses of misoprostol were identified; however low doses of misoprostol appear to be associated with fewer side-effects while moderate doses appear to be more efficient in completing abortion. Four RCTs showed that the induction to abortion interval with 3-hourly vaginal administration of prostaglandins is shorter than 6-hourly administration without an increase in side-effects.

Many studies reported the need for surgical evacuation. Indications for surgical evacuation include retained products of the placenta and heavy vaginal bleeding. Fewer women required surgical evacuation when misoprostol was administrated vaginally compared with women receiving intra-amniotical PGF_{2a}. Mild, self-limiting diarrhoea was more common among women who received misoprostol compared to other agents.

Authors' conclusions

Medical abortion in the second trimester using the combination of mifepristone and misoprostol appeared to have the highest efficacy and shortest abortion time interval. Where mifepristone is not available, misoprostol alone is a reasonable alternative. The optimal route for administering misoprostol is vaginally, preferably using tablets at 3-hourly intervals. Apart from pain, the side-effects of vaginal misoprostol are usually mild and self limiting. Conclusions from this review are limited by the gestational age ranges and variable medical regimens, including dosing, administrative routes and intervals of medication, of the included trials.

PLAIN LANGUAGE SUMMARY

Planned abortion after three months of pregnancy can be done using several medicines. This review looked at which medical procedure is the best.

There are many medical methods for planned termination of pregnancy in the second trimester of pregnancy (abortion after three months). We did a search of the scientific literature to find out which is the best method. We identified 38 studies and came to the conclusion that misoprostol is the drug of choice for medical pregnancy termination, preferably in combination with mifepristone which facilitates the effectiveness of misoprostol. Misoprostol works best when it is administered into the vagina. Women who had previously given birth could take misoprostol by mouth (under the tongue). Irrespective of the medication used for second trimester termination there is a considerable risk of surgical intervention because of vaginal bleeding or incomplete abortion.

BACKGROUND

With the wide-scale introduction of prenatal screening programmes the issue of second trimester abortion has become increasingly relevant, in particular for women whose pregnancies are complicated by a serious fetal anomaly (Asch 1999; Ballantyne 2009; Boyd 2008). Additionally, there are many reasons other than fetal anomalies for which women seek abortion in the midtrimester (Drey 2006; Grimes 1998; Ingham 2008). Second trimester abortion for fetal structural anomalies may have advantages over surgical abortion as it is operator independent and the intact fetus may be preferable for feto-pathological examination (Akgun 2007; Isaksen 1998; Isaksen 1999; Kaasen 2006). Medical abortion, however, also has several limitations including the need for the hospitalisation, the need for surgical removal of (the retained products of) the placenta when indicated, and the emotional impact of the process of labor and delivery on women who choose to end a pregnancy.

Medical abortion in the first trimester of pregnancy is considered successful if complete expulsion of the conceptus occurs without the need for surgical intervention (Christin-Maitre 2000). Beyond the first trimester, definitions differ but generally consider expulsion of the fetus separate from management of the placenta.

Several regimens for second trimester abortion have been published. Most of these are based on misoprostol or gemeprost, which are synthetic prostaglandin E_1 analogues (PGE_1), and used alone or misoprostol combined with mifepristone. Comparison of medical methods with surgical evacuation for mid-trimester termination of pregnancy is the subject of another review (Lohr 2008).

Agents used for medical abortion

Prostaglandins

Prostaglandins and their analogues are widely used for medical termination of pregnancy. Prostaglandins are produced by almost every tissue in the body and play a major role in human reproduction and in many other vital processes. To date, nine groups (A, B, C, D, E, F, G, H, I) and three types (PG1, PG2, PG3) of prostaglandins have been identified. Prostaglandins of the F and E series are the most important prostaglandins involved in pregnancy, labor, delivery and puerperium. PG receptors are always present in myometrial tissue.

Misoprostol (PGE_1) is increasingly used for second trimester termination of pregnancy (Friedman 2001; Goldberg 2001; Wagner 2005; Weeks 2005). Misoprostol is marketed for use in the prevention and treatment of peptic ulcer disease, and it is registered for obstetric indications, including abortion, in a few countries. It is inexpensive, stable at room temperature and it is rapidly absorbed by vaginal, sublingual, buccal and oral routes (Tang 2002; Zieman 1997). Moreover, misoprostol is reportedly associated with few, relatively minor side-effects. Serious complications such as uterine rupture are rare.

Gemeprost (PGE_1) is formulated as a vaginal suppository which requires refrigeration, and is not as widely available as misoprostol. Like other prostaglandins, it induces uterine contractions and cervical softening.

Dinoprost ($PGF_{2\alpha}$) and dinoprostone (PGE_2) are natural prostaglandins which induce uterine activity and are available for intravenous, intra-amniotic and extra-amniotic use.

Carboprost (15 methyl $PGF_{2\alpha}$) can be given by intramuscular or intra-amniotic injection and its methyl ester can be given as vaginal suppository. Carboprost and its methyl ester are both effective in inducing uterine contractions.

Sulprostone (PGE_2) is used intravenously. The intramuscular preparation of sulprostone is no longer available because it was associated with cardiovascular complications, such as acute myocardial infarction and hypotension (Ulmann 1992).

Uterotonic agents other than prostaglandins

Mifepristone, also known as RU 486 or RU 38486, is a 19-norsteroid that specifically blocks the receptors for progesterone and glucosteroids. It is used as pretreatment 24 to 48 hours prior to the induction of first trimester abortion with a prostaglandin analogue. It sensitizes the myometrium of the uterus to prostaglandin (Belanger 1981; Bygdeman 1985; Norman 1992; Swahn 1988).

Oxytocin is released physiologically by the posterior pituitary and stimulates uterine contractions. The sensitivity of the uterus to oxytocin increases with gestational age.

Injection techniques

Intra-amniotic instillation

Several chemical solutions for intra-amniotic injection techniques have been used, including formalin, glucose, hypertonic saline, urea and $PGF_{2\alpha}$. When using hypertonic saline, a spinal needle is passed through the abdominal wall into the amniotic cavity. A variable amount of the amniotic fluid surrounding the fetus is removed and replaced by 150 to 250 ml of 20% saline chloride solution that will induce abortion (Bygdeman and Gemzell-Danielsson 2008).

Extra-amniotic instillation

Instead of passing a spinal needle directly into the amniotic sac, effective irritants, such as ethacridine lactate or $PGF_{2\alpha}$, can be introduced through the cervix into the extra-amniotic space, that is, the space between the uterine wall and the fetal membranes. Ethacridine lactate is an organic compound based on acridine. Its primary use is as an antiseptic in solutions of 0.1%. When used as an agent for second trimester abortion, it is thought to stimulate endogenous prostaglandin production and subsequent uterine contractions. Up to 150 ml of 0.1% ethacridine is instilled into the extra-amniotic space using a Foley catheter. Oxytocin intravenous administration is often used concomitantly to expedite fetal expulsion (Bygdeman and Gemzell-Danielsson 2008).

Description of the problem or issue

Second trimester abortions constitute 10% to 15% of all induced abortions worldwide but are responsible for two-thirds of major abortion-related complications (Drey 2006; Grimes 1998). Medical methods for second trimester induced abortion have improved considerably during the last decades in terms of efficacy and safety; however, a variety of regimens remain in use.

Why it is important to do this review

Because of improved ultrasound technology, the prenatal detection of fetal structural anomalies during the second trimester of pregnancy has improved substantially. For this reason, the demand for medical methods to terminate pregnancy during the second trimester has also increased (Grimes 1998). Additionally, there are a number of other reasons why women seek abortion in the mid-trimester. There are many medical regimens for mid-trimester termination of pregnancy. This review aims to identify the most effective medical regimens for mid-trimester abortion with the fewest side-effects.

OBJECTIVES

To evaluate the medical regimens for second trimester medical abortion in terms of efficacy and side-effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials were considered for inclusion if different medical methods, routes of application or doses used for second trimester medical abortion were compared.

Types of participants

Studies which included healthy women undergoing a second trimester abortion were eligible if carrying a singleton, living fetus between 12 to 28 weeks gestation. Studies including women with multiple pregnancies, or those who had cervical preparation prior to the abortion procedure were excluded.

Types of interventions

Different medical methods, administration routes or doses of medication used for second trimester medical abortion.

Types of outcome measures

The main outcome measures were the induction to abortion interval and the number of complete abortions within 24 hours. The primary endpoint for the abortion interval is expulsion of the fetus. The secondary endpoint for the abortion interval is the expulsion of the placenta. In addition, other secondary outcome measures included the need for surgical evacuation (non-emergency procedure, emergency procedure, or not specified, including manual removal of the placenta), blood loss (measured, need for blood transfusion or clinically relevant drop in haemoglobin), uterine rupture, pain resulting from the procedure (reported by the women or measured by use of analgesics), nausea, vomiting and diarrhoea. The table Characteristics of included studies includes whether a surgical intervention was performed routinely in the study.

Potential confounding

The sensitivity of the myometrium for uterotonic drugs increases with gestational age. Hence, the longer the gestation, the less uterotonic drugs are needed. Apart from gestational age, parity could also be viewed as a potential confounder as multiparous women appear to have a shorter time interval to abortion. Differential treatment effects could theoretically be ascribed by differences in gestational age or parity. Parity and gestational age of study participants are listed under Characteristics of included studies.

Search methods for identification of studies

See:Collaborative Review Group search strategy.

The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE and Popline were systematically searched. Reference lists of retrieved papers were searched. Electronic literature search was conducted using the following key words: (induced abortion) AND (second trimester) AND (mifepristone OR misoprostol OR methotrexate OR dinoprost OR dinoprostone OR carboprost OR sulprostone OR gemeprost OR meteneprost OR epostane OR oxytocin OR RU 486 OR mifegyne) OR ethacridine lactate AND ((randomised controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR ("latin square" [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]))

Data collection and analysis

Selection of studies

The selection of trials for inclusion was performed independently by two review authors after employing the research strategy described previously. Trials under consideration were evaluated for inclusion and methodological quality without consideration of the results. This review is limited to randomised controlled trials, thereby focusing on four types of medical interventions for second trimester termination of pregnancy, that is (1) mifepristone and prostaglandin, (2) misoprostol, (3) other prostaglandins and (4) hyperosmolar agents (hypertonic saline, ethacridine lactate).

A form was designed to facilitate the process of data extraction which was performed by two of the reviewers independently. There were no discrepancies between the reviewers in either decision of inclusion/exclusion of studies or in data extraction.

Trials were not excluded based on an arbitrary cut-off limit regarding losses to follow up. Subgroup analyses were planned for early and late second trimester abortions as the performance of methods may differ with gestational age.

Trials describing the use of quinine were excluded. Trials including more than 20% fetal death at the onset of treatment (unless separate analysis was available), multiple pregnancies, women with uterine scars (if reportedly included in the trial) and regimens which included cervical preparation prior to the abortion procedure were excluded.

Data extraction and management

Data were extracted by two authors from eligible studies. Study characteristics (type of study, allocation, blinding), participants characteristics (number, gestational age), interventions, main

outcome measures and results were recorded. An attempt was made to obtain additional information from authors if required.

Assessment of risk of bias in included studies

The quality of studies was assessed without blinding to authorship or journal. Bias was assessed using the following.

1. Allocation concealment. The quality score for concealment of allocation was assigned to each trial using the criteria in the Cochrane Handbook:

A adequate concealment of allocation;

B unclear whether adequate concealment of allocation;

C inadequate concealment of allocation (includes quasi-randomised studies.

Only trials scoring A or B were included in the review.

2. Blinding of participants, clinicians and investigators.

3. Protection against exclusion bias.

4. Appropriate analysis of data.

Assessment of heterogeneity

Heterogeneity was analysed using the I^2 statistic (Higgins 2003). I^2 values of 25%, 50%, and 75% correspond to low, medium and high levels of heterogeneity.

Data synthesis

Data analyses was performed by using Revman 5 software.

Trials that were conducted within the subject of this review included the comparison of different medical methods, application methods and dose regimens. For this reason, the trials were considered by medical regimen comparing the outcome measures for each regimen as described earlier. The different comparisons are as follows.

Comparison 1: mifepristone + misoprostol versus mifepristone + gemeprost.

Comparison 2: mifepristone + misoprostol versus misoprostol alone.

Comparisons 3 to 5: routes of administration of misoprostol combined with mifepristone:

- Comparison 3: vaginal use versus the oral use of misoprostol;
- Comparison 4: vaginal use versus the sublingual use of misoprostol;
- Comparison 5: oral use versus the sublingual use of misoprostol.

Comparison 6: dosing interval of misoprostol following mifepristone.

Comparison 7: dosing of mifepristone previous to misoprostol.

Comparison 8: combined regimen of mifepristone + gemeprost.

Comparisons 9 to 11: misoprostol versus another prostaglandin:

- Comparison 9: misoprostol versus intra-amniotic $PGF_{2\alpha}$;
- Comparison 10: misoprostol versus gemeprost;
- Comparison 11: misoprostol versus dinoprostone.

Comparisons 12 to 13: routes of administration of misoprostol:

- Comparison 12: vaginal use versus the oral use of misoprostol;
- Comparison 13: vaginal use versus the sublingual use of misoprostol.

Comparison 14: misoprostol tablet insertion versus gel insertion.

Comparisons 15 to 16: time interval for repeat dosing of misoprostol or gemeprost:

- Comparison 15: Time interval of misoprostol;
- Comparison 16: Time interval of gemeprost.

Comparison 17: low dose versus a higher dose of misoprostol.

Comparisons 18 to 19: prostaglandin E_2 versus prostaglandin $F_{2\alpha}$:

- Comparison 18: prostaglandin E_2 versus prostaglandin $F_{2\alpha}$;
- Comparison 19: prostaglandin E_2 versus prostaglandin $F_{2\alpha}$ + oxytocin.

Comparison 20: intra-amniotic instillation of prostaglandin $F_{2\alpha}$ versus intra-amniotic instillation of hypertonic saline (20%).

Comparison 21: combined regimen intra-amniotic prostaglandin $F_{2\alpha}$ + hypertonic saline.

Comparison 22: prostaglandin E_1 vaginally versus the intra-amniotic instillation of prostaglandin $F_{2\alpha}$ + hypertonic saline.

Comparison 23: prostaglandins versus ethacridine lactate.

Comparison 24: ethacridine lactate versus normal saline.

RESULTS

Description of studies

See: Characteristics of included studies;Characteristics of excluded studies

Results of the search

Eighty-eight studies underwent full review. Full text review excluded 52 studies as they were not randomised; used inadequate concealment (score C); included over 20% fetal demise, multiple pregnancies, patients with uterine scarring; a pre-treatment trial, including medical or mechanical dilatation of the cervix. See Characteristics of excluded studies.

Forty studies were included in this review. Due to the diversity of the interventions, the review concerns the comparison of 24 regimens. Three trials compared more than two different groups and the interventions are therefore listed as different comparisons (Mehta 1975 a; Mehta 1975 b; Muzsnai 1979 a; Muzsnai 1979 b; Muzsnai 1979 c; Muzsnai 1979 d; Nuutila 1997 a; Nuutila 1997 b; Nuutila 1997 c). The main outcomes considered were induction to abortion interval or completed abortion within 24 hours.

Included studies

Four studies (Borgida 1995; Ho 1996; Nielsen 1975; Steyn 1993) each enrolled 50 patients or less.

Four separate interventions were used.

1. Mifepristone and prostaglandin

- Three studies (210 patients) compared a regimen of mifepristone and misoprostol to mifepristone and gemeprost (Bartley 2002; el-Refaey 1993; Ho 1996).
- One study (64 patients) compared mifepristone to a placebo prior to misoprostol induced abortion (Kapp 2007).
- Five studies (500 patients) compared different routes of administration of misoprostol combined with mifepristone:
  - vaginal use compared to oral use (306 patients) (El-Refaey 1995; Ho 1997; Ngai 2000);
  - vaginal use compared to sublingual use (76 patients) (Hamoda 2005);
  - oral use compared to sublingual use (118 patients) (Tang 2005).
- One study (141 patients) compared the dosing interval of misoprostol following mifepristone administration (Chai 2009).
- One study (70 patients) compared the dosage of mifepristone before misoprostol was administered (Webster 1996).
- One study (100 patients) compared 0.5mg and 1.0 mg gemeprost combined with mifepristone (Thong 1996).

2. Misoprostol

- Five studies (693 patients) compared misoprostol to another prostaglandin:
  - one studies (125 patients) compared the vaginal use of misoprostol to PGF2α (Su 2005);
  - two studies (221 patients) compared the vaginal use of misoprostol to gemeprost (Nuutila 1997 a; Nuutila 1997 b; Wong 1998);
  - one study (130 patients) compared the vaginal use of misoprostol to dinoprostone (Makhlouf 2003).
- Five studies (812 patients) compared different routes of administration of misoprostol:
  - vaginal use compared to oral use (310 patients) (Akoury 2004; Bebbington 2002; Behrashi 2008);
  - vaginal use compared to sublingual use (502 patients) (Bhattacharjee 2008; Tang 2004; von Hertzen 2009).
- One study (148 patients) compared misoprostol tablets to gel insertion (Pongsatha 2008).
- Three studies (427 patients) compared different time intervals of misoprostol or gemeprost (Armatage 1996; Herabutya 2005; Wong 2000).
- Two studies (133 patients) compared different doses of misoprostol (Nuutila 1997 c; Ozerkan 2009).

2. Other prostaglandins

- Three studies (143 patients) compared prostaglandin E_2 to prostaglandin $F_{2\alpha}$ (Borgida 1995; Sorensen 1984; Steyn 1993).

3. Hyperosmolar agents

- Four studies (1670 patients) compared hypertonic saline and prostaglandin $F_{2\alpha}$ (Faktor 1988; Mehta 1975 a; Mehta 1975 b; Nielsen 1975; WHO 1976).
- One study (385 patients) compared different regimens of prostaglandin $F_{2\alpha}$ and hypertonic saline (Muzsnai 1979 a; Muzsnai 1979 b; Muzsnai 1979 c; Muzsnai 1979 d).
- One study (58 patients) compared gemeprost to prostaglandin $F_{2\alpha}$ and hypertonic saline (Waldron 1990).
- Three studies (302 patients) compared prostaglandins to ethacridine lactate (Inan 1997; Kelekci 2006; Olund 1978).
- One study (37 patients) compared ethacridine lactate to normal saline (Zauva 1989).

Risk of bias in included studies

Only randomised controlled trials were included in this review. Thirty-two studies reported the method of randomisation (Akoury 2004; Armatage 1996; Bartley 2002; Bebbington 2002; Bhattacharjee 2008; Borgida 1995; Chai 2009; el-Refaey 1993; El-refaey 1995; Hamoda 2005; Herabutya 2005; Ho 1996; Ho 1997; Kapp 2007; Kelekci 2006; Makhlouf 2003; Mehta 1975 a; Mehta 1975 b; Ngai 2000; Nuutila 1997 a; Nuutila 1997 b; Nuutila 1997 c; Ozerkan 2009; Pongsatha 2008; Sorensen 1984; Steyn 1993; Su 2005; Tang 2004; Tang 2005; Thong 1996; von Hertzen 2009; Webster 1996; WHO 1976; Wong 1998; Wong 2000). For more detailed information, see the section Included studies. Eleven studies did not state the inclusion or exclusion criteria (Bartley 2002; el-Refaey 1993; El-refaey 1995; Faktor 1988; Inan 1997; Mehta 1975 a; Mehta 1975 b; Nielsen 1975; Nuutila 1997 a; Nuutila 1997 b; Nuutila 1997 c; Olund 1978; Ozerkan 2009; Webster 1996).

Allocation

Allocation concealment was adequately reported in 28 studies (Akoury 2004; Armatage 1996; Bartley 2002; Bebbington 2002; Bhattacharjee 2008; Borgida 1995; Chai 2009; el-Refaey 1993; El-refaey 1995; Hamoda 2005; Herabutya 2005; Ho 1996; Ho 1997; Kapp 2007; Makhlouf 2003; Mehta 1975 a; Mehta 1975 b; Ngai 2000; Nuutila 1997 a; Nuutila 1997 b; Nuutila 1997 c; Steyn 1993; Su 2005; Tang 2004; Tang 2005; Thong 1996; von Hertzen 2009; Webster 1996; WHO 1976; Wong 1998; Wong 2000).

Blinding

Blinding (no further explanation was given) was reported in one study (von Hertzen 2009). Blinding of participants was reported in one study (Ngai 2000). Blinding of participants and clinicians was reported in two studies (Ho 1997; Tang 2005). Blinding of participants, clinicians and researchers was reported in one study (Kapp 2007).

Effects of interventions

For outcomes using a continuous scale, the mean difference (MD) with 95% confidence intervals (95% CI) were used to asses the effects of the intervention. For dichotomous outcomes the results were expressed using odds ratio (OR) with 95% confidence intervals (95% CI).

Comparison 1: combined regimen mifepristone + misoprostol versus mifepristone + gemeprost

Three trials (Bartley 2002; el-Refaey 1993; Ho 1996) were included in this comparison. In total, 210 women were eligible for analysis.

In regards to the induction to abortion interval, el-Refaey 1993 did not provide standard deviations, and thus precluded inclusion of these data in the meta-analysis. The median induction to abortion interval was 8 hrs (range 1 to 60) and 9.1 hrs (range 3 to 22) for the oral use of 400 µg misoprostol and the 1 mg gemeprost pessaries group respectively (not significant). There were no significant differences in the induction-to-abortion interval (Analysis 1.1), abortion rate within 24 hours (Analysis 1.2), need for surgical evacuation (Analysis 1.3) or side-effects (pain, Analysis 1.4; nausea, Analysis 1.5; vomiting, Analysis 1.6; diarrhoea, Analysis 1.7) between regimens using mifepristone with either misoprostol or gemeprost.

Comparison 2: misoprostol versus mifepristone + misoprostol

One trial (Kapp 2007) was included in this comparison. In this regimen, 64 women were eligible for analysis. Women who received mifepristone + misoprostol aborted more rapidly than women who had misoprostol alone (Analysis 2.1) (MD 12.13, 95% CI 1.43 to 102.61). No difference was found in terms of the need for surgical evacuation (Analysis 2.2), pain (Analysis 2.3), vomiting (Analysis 2.5) or nausea (Analysis 2.4).

Comparisons 3 to 5: routes of administration of misoprostol combined with mifepristone

In this comparison, five trials with three comparisons (El-refaey 1995; Hamoda 2005; Ho 1997; Ngai 2000; Tang 2005) were included.

Comparison 3: vaginal use compared to oral use of misoprostol

In this comparison, three trials (El-refaey 1995; Ho 1997; Ngai 2000) were included. In total, 306 women were eligible for analysis. The largest trial in this analysis was conducted by Ngai, comparing the oral use of 400 µg and the vaginal use of 200 µg of misoprostol, both combined with 200 mg mifepristone administered orally 36 to 48 hours in advance. In addition to this comparison, both groups received either vaginal or oral placebo tablets. Ho 1997 conducted a randomised controlled trial comparing the use of 200 µg of misoprostol orally combined with a vaginal placebo to the vaginal use of 200 µg misoprostol combined with an oral placebo, each arm combined with 200 mg mifepristone. The vaginal use of 200 µg misoprostol was superior (MD 13.00, 95% CI 2.77 to 23.23) to the oral use of 200 µg misoprostol (Analysis 3.1). When both oral and vaginal misoprostol was administered in a low dose (200 µg), the vaginal use was superior to the oral use regarding the abortion rate within 24 hours (Analysis 3.2) (OR 0.26, 95% CI 0.09 to 0.78). In regards to the induction-to-abortion interval, El Refaey 1995 did not provide a standard deviation in addition to estimates which precluded the inclusion of these data in the meta-analysis. The mean induction to abortion interval was 6.0 hrs (95% CI 5.0 to 7.2) and 6.7 hrs (95% CI 5.8 to 7.6) for the oral and the vaginal groups respectively (not significant). No significant difference was found between the oral and vaginal use of misoprostol in terms of induction-to-abortion interval. In addition, no difference was found between the need for surgical evacuation (Analysis 3.3), amount of pain (Analysis 3.4), nausea (Analysis 3.5) or vomiting (Analysis 3.6). However, fewer episodes of diarrhoea occurred (Analysis 3.7) (OR 2.21, 95% CI 1.06 to 4.61) when 200 µg misoprostol was administered vaginally compared to 400 µg misoprostol, orally.

Comparison 4: vaginal use compared to sublingual use of misoprostol

In this comparison, one trial (Hamoda 2005) was included. In total, 69 women were eligible for analyses. The comparison was made between the sublingual use of 600 µg of misoprostol and the vaginal use of 800 µg, both combined with 200 mg mifepristone. In regards to the induction-to-the abortion interval, no mean or SD was provided and thus precluded inclusion of these data in a meta-analysis. The median and range of the sublingual group (median 5.27, range 0.55 to 29.35) and of the vaginal group (median 5.40, range 2.10 to 13.00) showed no significant difference (P = 0.95) for the abortion interval. In addition, no difference between the sublingual and vaginal use was found in terms of the need for surgical evacuation (Analysis 4.1) or side-effects such as pain (Analysis 4.2), nausea (Analysis 4.3), vomiting (Analysis 4.4) or diarrhoea (Analysis 4.5).

Comparison 5: oral use compared to sublingual use of misoprostol

In this comparison, one trial (Tang 2005) was included. In total, 118 women were eligible for analysis. Tang 2005 compared the oral and sublingual use of 400 µg of misoprostol in combination with 200 mg of mifepristone. Both groups received oral or sublingual placebo tablets. In regards to the induction-to-the abortion interval, no mean or SD was provided and thus precluded inclusion of these data in a meta-analysis. The sublingual group (median 5.5, range 1.4 to 43.2) aborted in a shorter time interval when compared to the oral group (median 7.5, range 2.4 to 38.8) (P = 0.009). No difference was found in regards to the abortion rate within 24 hours (Analysis 5.1) or side-effects such as pain (Analysis 5.2), nausea (Analysis 5.3) or diarrhoea (Analysis 5.4).

Comparison 6: dosing interval of misoprostol following mifepristone administration

One trial (Chai 2009) was included in this comparison. There were 141 women eligible for analyses. No difference was found in the abortion rate within 24 hours (Analysis 6.1), need of surgical evacuations (Analysis 6.2), or side-effects of pain (Analysis 6.3), nausea (Analysis 6.4) and diarrhoea (Analysis 6.5). All patients from one centre had dilatation and curettage the day following abortion, as it was the routine practice in that hospital. These patients were not included in Analysis 6.2.

Comparison 7: dose of mifepristone before the administration of misoprostol

One trial (Webster 1996) was included in this comparison. In total, 70 women were eligible for analyses. No difference was found in the induction of the abortion interval (Analysis 7.1), abortion rate within 24 hours (Analysis 7.2), need of surgical evacuation (Analysis 7.3) or side-effects of pain (Analysis 7.4), vomiting (Analysis 7.5) or diarrhoea (Analysis 7.6).

Comparison 8: regimen mifepristone + gemeprost 1.0 mg versus mifepristone + gemeprost 0.5 mg

One trial (Thong 1996) was included in this comparison. There were 100 women eligible for analysis. No difference was found in the abortion rate within 24 hours (Analysis 8.1), excessive blood loss (Analysis 8.2), need for surgical evacuation (Analysis 8.3) or episodes of diarrhoea (Analysis 8.5). When patients were given 0.5

mg gemeprost rather than 1 mg, they experienced fewer episodes of vomiting (Analysis 8.4) (OR 2.83, 95% CI 1.04 to 7.66).

Comparisons 9 to 11: misoprostol versus another prostaglandin

Four trials with seven comparisons (Makhlouf 2003; Nuutila 1997 a; Nuutila 1997 b; Su 2005; Wong 1998) were included. Nuutila compared three interventions, that is, two doses of vaginal misoprostol and vaginal gemeprost. For this reason, this trial was considered for each of the different comparisons (see Characteristics of included studies).

Comparison 9: misoprostol versus intra-amniotic $PGF_{2\alpha}$

In this comparison, one trial was included (Su 2005). In total, 125 women were eligible for analysis. Su 2005 compared the use of vaginal misoprostol with the use of intra-amniotic PGF2α. Vaginal misoprostol was superior to intra-amniotic $PGF_{2\alpha}$ (MD -4.60, 95% CI -7.74 to -1.46) (Analysis 9.1) regarding the induction to the abortion interval. No difference was found between the groups in relation to the abortion completion rate (Analysis 9.2), need for surgical evacuations (Analysis 9.3), nausea (Analysis 9.4), vomiting (Analysis 9.5) or diarrhoea (Analysis 9.6).

Comparison 10: misoprostol versus PGE_1 (gemeprost)

In this comparison, two trials with three comparisons were included (Nuutila 1997 a; Nuutila 1997 b; Wong 1998). In total, 249 women were eligible for analysis. The largest trial in this analysis was conducted by Wong 1998, comparing the vaginal use of misoprostol, 400 µg every 4 hours, to the vaginal use of gemeprost. When misoprostol was used at very low doses (100 µg) (MD 8.60, 95% CI 3.11 to 14.09) or 200 µg (MD 13.30, 95% CI 7.90 to 18.70) every 6 or 12 hours, respectively, gemeprost was superior (Analysis 10.1). In contrast, when misoprostol was used at a higher dose (400 µg) (OR 2.83, 95% CI 1.33 to 6.02) every 3 or 6 hours, more women aborted within 24 hours in comparison to gemeprost (Analysis 10.2). In regards to the side-effects, women who received misoprostol experienced less pain (100 µg) (OR 0.22, 95% CI 0.07 to 0.71) or 200 µg (OR 0.23, 95% CI 0.07 to 0.77), vomiting (misoprostol 200 µg, OR 0.15, 95% CI 0.04 to 0.62) and diarrhoea (100 µg, OR 0.04, 95% CI 0.00 to 0.68) or 200 µg (OR 0.18, 95% CI 0.03 to 0.91) (Analysis 10.5; Analysis 10.7; Analysis 10.8). Moreover, the amount of blood loss was decreased when women received 200 µg misoprostol when compared to gemeprost (Analysis 10.3) (OR -146.00, 95% CI -219.02 to -72.98). No difference was found between the groups in relation to the need for surgical evacuation (Analysis 10.4) or nausea (Analysis 10.6).

Comparison 11: misoprostol versus PGE_2 (dinoprostone)

In this comparison, one trial was included (Makhlouf 2003). In total, 80 women were eligible for analysis. More women who were given misoprostol, 100 µg every four hours, aborted within 24 hours when compared to PGE_2, 6 mg every six hours (Analysis 11.1) (OR 51.73, 95% CI 2.89 to 924.42). There was no difference regarding blood loss (Analysis 11.2), need for surgical evacuation (Analysis 11.3) or side-effects of pain (Analysis 11.4), vomiting (Analysis 11.5) or diarrhoea (Analysis 11.6) between the groups.

Comparisons 12 to 13: routes of misoprostol for misoprostol used alone

In this comparison, six trials with two comparisons (Akoury 2004; Bebbington 2002; Behrashi 2008; Bhattacharjee 2008; Tang 2004; von Hertzen 2009) were included.

Comparison 12: vaginal use of misoprostol versus the oral use of misoprostol

In this comparison, three trials were included (Akoury 2004; Bebbington 2002; Behrashi 2008). In total, 310 women were eligible for analysis. The largest trial was conducted by Akoury, comparing the oral and vaginal use of misoprostol and the intra-amniotic use of $PGF_{2\alpha}$. The vaginal administration of misoprostol was superior to the oral route (Analysis 12.1), at both a lower dose (200 µg) (mean difference (MD) -14.90, 95% CI -23.33 to -6.47) and a higher dose (400 µg) (MD -6.04, 95% CI -8.51 to -3.58). The abortion rate after 24 hours with vaginal use was also superior to the oral use of 200 µg of misoprostol (OR 9.60, 95% CI 3.74 to 24.66) (Analysis 12.2). Fewer women experienced nausea when the misoprostol was given vaginally when compared to the oral use of 400 µg of misoprostol (Analysis 12.6) (OR 0.41, 95% CI 0.18 to 0.93). No difference was found between the groups in regard to the amount of blood loss (Analysis 12.3), pain (Analysis 12.4), need for surgical evacuation (Analysis 12.5), vomiting (Analysis 12.7) or diarrhoea (Analysis 12.8).

Comparison 13: vaginal use of misoprostol versus the sublingual use of misoprostol

In this comparison, three trials were included (Bhattacharjee 2008; Tang 2004; von Hertzen 2009). In total, 1178 women were eligible for analysis. The largest trial was conducted by von Hertzen, comparing the vaginal use of 400 µg misoprostol to the sublingual use of 400 µg misoprostol with the use of placebo tablets. No difference was found between the vaginal or the sublingual use of misoprostol for the induction to abortion interval in one smaller study (Analysis 13.1). Von Hertzen was not included in this analyses, because no mean (SD) was provided. However, authors did provide median (range). In the vaginal group, the induction to abortion interval was longer (median 12.3, range 3.2 to 48.0) than the sublingual group (median 12.0, range 4.1 to 61.8). However, this difference was not significant. The abortion rate after 24 hours with vaginal use was superior to the sublingual use (Analysis 13.2) (OR 1.39, 95% CI 1.05 to 1.83). However, the significant heterogeneity for the analysis (Analysis 13.2) (I^2 = 63%) must be noted despite use of identical regimens precludes confidence in these combined estimates. The heterogeneity between these data could potentially be explained by the difference in included numbers of multigravidas between both trials; Tang included 36% to 39%, while Bhattacharjee included 80% of women studied. Because of the possibility that among nulliparous women, vaginal misoprostol is associated with higher rates of complete abortion within 24 hours, the analysis were separated. Vaginal misoprostol is associated with significantly higher rates of complete abortion within 24 hours among nulliparous women (OR 2.31, 95% CI 1.17 to 4.54), while among multiparous women, there is no difference between vaginal or sublingual administration (OR 0.90, 95% CI 0.55 to 1.47). Von Hertzen conducted a stratified analysis by parity because there was a highly significant interaction of treatment by parity. When success rates at 24 h were analysed according to parity, vaginal administration was clearly superior to sublingual administration in nulliparous women (87.3% versus 68.5%) but

the difference between treatments was not present among parous women: 84.7% (vaginal) versus 88.5% (sublingual).

No differences were noted in the meta-analysis for the occurrence of complications of blood loss (Analysis 13.3) or surgical evacuations (Analysis 13.5) or side-effects of pain (Analysis 13.4), nausea (Analysis 13.6), vomiting (Analysis 13.7) or diarrhoea (Analysis 13.8).

Comparison 14: misoprostol tablet insertion versus gel insertion

One trial (Pongsatha 2008) was included in this comparison. For analysis, 148 women were eligible for analysis. In terms of adverse outcomes, women who had misoprostol inserted with gel experienced more diarrhoea (Analysis 14.7) (OR 0.15, 95% CI 0.03 to 0.71). No significant difference was observed between the two groups in terms of abortion within 24 hours (Analysis 14.1), excessive blood loss (Analysis 14.2), need for surgical evacuation (Analysis 14.3), pain (Analysis 14.4), nausea (Analysis 14.5) or vomiting (Analysis 14.6).

Comparisons 15 to 16: time interval and dose of misoprostol or gemeprost

Four trials with two comparisons (Armatage 1996; Herabutya 2005; Wong 2000) were included.

Comparison 15: time interval of misoprostol

Two trials (Herabutya 2005; Wong 2000) were included in this comparison. In total, 427 women were eligible for analysis. The largest trial in this analysis was conducted by Wong 2000 who examined the optimal time interval for the vaginal use of 400 µg misoprostol, either administered every three or every six hours. When the time interval was shorter, the interval to abortion was shorter (three hours) (Analysis 15.1) (MD -19.20, 95% CI -36.02 to -2.38) compared to the longer time interval (six hours). In regards to the induction to abortion interval, no mean or SD was provided by Herabutya 2005 and thus precluded inclusion of these data in the meta-analysis. The median induction-to-abortion interval was 15.8 hrs (25, 75 centiles: 12, 26) and 16.0 hrs (25, 75 centiles: 12, 30) for the group given misoprostol with a shorter time interval and the group with a longer time interval respectively (P =0.80). No effect was found for the time interval in relation to the abortion rate within 24 hours (Analysis 15.2), excessive blood loss (Analysis 15.3; Analysis 15.4), need for surgical evacuation (Analysis 15.5), or side-effects of pain (Analysis 15.6), nausea (Analysis 15.7), vomiting (Analysis 15.8) or diarrhoea (Analysis 15.9).

Comparison 16: time interval of gemeprost

One trial (Armatage 1996) was included in this comparison. In total, 99 women were eligible for analysis. In regards to the induction to abortion interval, no mean or SD was given, and thus precluded inclusion of these data in a meta-analysis. The median induction-to-abortion interval was 16 hrs (25, 75 centiles: 12, 26) and 15 hrs (25, 75 centiles: 11.4, 28.5) for the group given gemeprost with a shorter time interval compared with the longer time interval, respectively (not significant). In addition, no significant difference was found between both groups in the abortion rate after 24 hours (Analysis 16.1), need for surgical evacuation (Analysis 16.2) or pain (Analysis 16.3).

Comparison 17: low dose versus a higher dose of misoprostol

Two trials (Nuutila 1997 c; Ozerkan 2009) were included in this comparison. In total, 133 women were eligible for analyses. Ozerkan 2009 compared the use of 600 µg with the use of 400 µg of misoprostol. An initial first dose of 600 µg of misoprostol was found to be more effective than 400 µg (Analysis 17.1) (MD 6.40, 95% CI 0.40 to 12.40). While gestational age or parity were not found to be related to the duration of the termination procedure, a higher parity was shown to be correlated with a shorter induction to fetal-expulsion period in the low dose, but not in the high dose group. Nuutila 1997 c compared the use of 100 µg of misoprostol to the use of 200 µg of misoprostol. The study found no difference between these groups in terms of the induction of the abortion interval (Analysis 17.1). The significant heterogeneity for the analysis (Analysis 17.1) (I^2 = 84%) must be noted. This is most likely do to the different misoprostol doses the trials used. Both studies found no difference in the amount of pain (Analysis 17.2), and side effects such as vomiting (Analysis 17.4) and diarrhoea (Analysis 17.5).

Comparisons 18 to 19: prostaglandin E_2 versus prostaglandin $F_{2\alpha}$

Three trials with two comparisons (Borgida 1995; Sorensen 1984; Steyn 1993) were included.

Comparison 18: prostaglandin E_2 versus prostaglandin $F_{2\alpha}$

One trial (Borgida 1995) was included in this comparison. In total, 50 women were eligible for analysis. When women were given prostaglandin E_2intravaginally, the interval to abortion was shorter (Analysis 18.1) (MD -9.10, 95% CI -13.68 to -4.52) when compared to the women receiving prostaglandin $F_{2\alpha}$ intramuscularly. In addition, more women given prostaglandin E_2 aborted within 24 hours (Analysis 18.2) (OR 11.29, 95% CI 1.29 to 98.89). No difference was found between the occurrence of side-effects of pain (Analysis 18.3), nausea (Analysis 18.4), vomiting (Analysis 18.5) or diarrhoea (Analysis 18.6).

Comparison 19: prostaglandin E_2 versus prostaglandin $F_{2\alpha}$ + oxytocin

Two trials (Sorensen 1984; Steyn 1993) were included in this comparison. In total, 59 women were eligible for analysis. In regards to the induction-to-abortion interval, Steyn 1993 did not provide SDs, and thus precluded inclusion of these data in a meta-analysis. The median induction to abortion interval was 38 hrs (range 19 to 61) and 23 hrs (range 11 to 54.5) for the intra-amniotic prostaglandin $F_{2\alpha}$ and the extra-amniotic prostaglandin E_2 group, respectively (not significant). When women were given prostaglandin E_2 + oxytocin, the interval to abortion was longer (Analysis 19.1) (MD 2.00, 95% CI 0.90 to 3.10) compared to the women receiving prostaglandin $F_{2\alpha}$ + oxytocin. Fewer surgical evacuations were performed in the prostaglandin E_2 + oxytocin group (Analysis 19.2) (OR 0.25, 95% CI 0.07 to 0.90) and fewer women experienced pain (Analysis 19.3) (OR 0.03, 95% CI 0.00 to 0.72) when compared to the use of prostaglandin $F_{2\alpha}$ + oxytocin. No difference was found regarding the episodes of vomiting or diarrhoea (Analysis 19.4; Analysis 19.5).

Comparison 20: intra-amniotic instillation of prostaglandin $F_{2\alpha}$ versus intra-amniotic instillation of hypertonic saline (20%)

Four trials (Faktor 1988; Mehta 1975 a; Mehta 1975 b; Nielsen 1975; WHO 1976) were included for analysis. In total, 1703 women were eligible for analysis. The largest trial in this analysis was conducted by the WHO 1976, comparing the intra-amniotic use of 25 mg of prostaglandin $F_{2\alpha}$ to the intra-amniotic instillation of 20% saline. In regards to the induction to abortion interval, Nielsen 1975. and the WHO trials did not provide standard deviations, and thus precluded inclusion of these data in a meta-analysis. The median induction to abortion interval in the study by Nielsen 1975 was 21.5 hrs (ranges not given) and 14.2 hrs (ranges not given) for the hypertonic saline and the $PGF_{2\alpha}$ group, respectively (P < 0.01). The median induction-to-abortion interval in the study by the WHO was 30.4 hrs (ranges not given) and 19.7 hrs (ranges not given) for the hypertonic saline and the $PGF_{2\alpha}$ group respectively (P <0.001). Based on analysis of only 25 women, a single dose of 40 mg prostaglandin $F_{2\alpha}$ proved to be more effective than 20% hypertonic saline in terms of induction-to- abortion interval (Analysis 20.1) (MD -5.30, 95% CI -6.67 to -3.93). The analysis of the abortion rate within 24 hours included 1678 women. Multiple doses of $PGF_{2\alpha}$ proved to be more effective than 20% hypertonic saline (Analysis 20.2) (OR 6.14, 95% CI 4.91 to 7.68). On the other hand, women who received hypertonic saline experienced fewer complications, such as the need for surgical evacuation (Analysis 20.8) (single dose of 50 mg $PGF_{2\alpha}$ OR 7.89, 95% CI 2.01 to 30.95; multiple doses of 25 mg $PGF_{2\alpha}$ OR 1.52, 95% CI 1.24 to 1.87) episodes of nausea (Analysis 20.5) (OR 3.01, 95% CI 1.17 to 7.72), vomiting (Analysis 20.6) (single dose of 50 mg $PGF_{2\alpha}$ OR 22.40, 95% CI 2.73 to 183.71; and multiple doses of 25 mg PGF OR 5.01, 95% CI 3.99 to 6.28) and diarrhoea (Analysis 20.7) (multiple doses of 25mg $PGF_{2\alpha}$ OR 12.47, 95% CI 6.81 to 22.82). The WHO trial reported more episodes of excessive blood loss in women receiving $PGF_{2\alpha}$ (Analysis 20.4) (OR 3.05, 95% CI 1.56 to 5.97).

Comparison 21: combined regimen prostaglandin $F_{2\alpha}$ and hypertonic saline

One trial (Muzsnai 1979 a; Muzsnai 1979 b; Muzsnai 1979 c; Muzsnai 1979 d) was included for analysis. In total, 770 women were eligible for analysis. The instillation of 25 ml 20% NaCl (5 g) + $PGF_{2\alpha}$ (20 mg) was superior to the instillation of 100 ml 10% NaCl (10 g) + $PGF_{2\alpha}$ (20 mg) (Analysis 21.1) in terms of the induction to the abortion interval (MD -2.96, 95% CI -5.29 to -0.64), but also in terms of the 24 hour abortion rate (OR 2.30, 95% CI 1.38 to 3.86) (Analysis 21.2). No significant difference was found between those who received 5 g of hypertonic saline versus 10 g in terms of excessive blood loss (Analysis 21.3), need for surgical evacuation (Analysis 21.4), vomiting (Analysis 21.6) and diarrhoea (Analysis 21.7). When given 25 ml of 20% hypertonic saline, women experienced less nausea (Analysis 21.5) (OR 0.33, 95% CI 0.17 to 0.62) than those who received 100 ml of 10% hypertonic saline.

Comparison 22: prostaglandin E1 (gemeprost) vaginally versus intra-amniotic instillation of prostaglandin $F_{2\alpha}$ + hypertonic saline

One trial (Waldron 1990) was included in this comparison. In total, 58 women were eligible for analysis. Women who had intra-amniotic instillation of prostaglandin $F_{2\alpha}$ + hypertonic saline aborted more rapidly than women who received vaginally administered gemeprost (Analysis 22.1) (MD 0.90, 95% CI 0.10 to 0.70) and the 24 hour abortion rate was significantly higher (Analysis 22.2) (OR 0.16, 95% CI 0.04 to 0.67). In addition, women who received gemeprost experienced more episodes of vomiting (Analysis 22.6) (OR 3.11, 95% CI 1.06 to 9.08) and diarrhoea (Analysis 22.7) (OR 19.13, 95% CI 3.80 to 96.18). No significant difference was found in terms of excessive blood loss (Analysis 22.3), need for surgical evacuation (Analysis 22.4) or pain (Analysis 22.5).

Comparison 23: prostaglandins versus ethacridine lactate

Three trials (Inan 1997; Kelekci 2006; Olund 1978) were included in this comparison. For analyses, 302 women were eligible. No significant difference in induction to abortion interval was found (Analysis 23.1). Olund 1978 provided no standard deviation and could therefore not enter our analysis. The mean and range of the abortion interval of the ethacridine lactate group (29.9, 23.9 to 47.2) and of the prostaglandin $F_{2\alpha}$ group (26.7, 8.9 to 63.0) showed no significant difference. More women in the ethacridine lactate group aborted within 24 hours (Analysis 23.2) (OR 0.18, 95% CI 0.06 to 0.48) in comparison to prostaglandin E2, but not in comparison to misoprostol. No differences were found in regard to the amount of blood loss (Analysis 23.3) or side-effects, such as nausea (Analysis 23.4), vomiting (Analysis 23.5) or diarrhoea (Analysis 23.6). Kelekci 2006 provided no information about the side-effects of each group, but found similar occurrences in both groups. Other side-effects described by Inan 1997 included endometritis (ethacridine lactate group 4.1%, PGE2 group 3.3%; difference not significant).

Comparison 24: ethacridine lactate versus normal saline

One trial (Zauva 1989) was included in this comparison. In total, 37 women were eligible for analysis. No differential effect was found between extra-amniotic ethacridine lactate and extra-amniotic normal saline regarding the induction-to-abortion interval (Analysis 24.1), excessive blood loss (Analysis 24.2), pain (Analysis 24.3), vomiting (Analysis 24.4) or rate of uterine rupture (Analysis 24.5).

DISCUSSION

Second trimester medical abortion regimens have evolved greatly over the past 20 years with increasing availability of prostaglandin analogues and anti-progesterone agents such as mifepristone. Older regimens such as instillation of hypertonic saline or prostaglandin $F_{2\alpha}$ although effective in provoking abortion, were associated with higher rates of serious adverse events than are modern methods (Bygdeman and Gemzell-Danielsson 2008).

Randomised comparisons included in this review demonstrate that misoprostol is the prostaglandin analogue of choice: it is as effective or more effective than other studied prostaglandins and has the preferable characteristics of heat stability and multiple administrative routes. However, in settings where prostaglandins are not available for second trimester medical abortion, extra-amniotic instillation of ethacridine lactate may be an alternative (Comparisons 23, 24) (Hou 2010). However, limited information is available percentage of women needing a surgical intervention for incomplete abortion and the safety outcomes of ethacridine lactate, given the small number of subjects studied. When using extra-amniotic instillation of drugs, the catheter tends to be expelled as the cervix dilates, before the abortion process is self-

sustaining. For this reason, supplementary infusions of oxytocin are commonly used (Kelekci 2006; WHO technical report series) which also increases the associated costs. Furthermore, intra-amniotic injection of drugs is potentially dangerous as accidental injection into maternal tissue or placenta can result in local tissue damage or harmful absorption into the maternal circulation (WHO technical report series). For this reason, the drugs should only be given by skilled operators. Intra-amniotic injection of drugs may also induce infection into the amniotic cavity (WHO technical report series).

Misoprostol when used alone is an effective inductive agent; however, it appears more efficient when combined with mifepristone, although the evidence from randomised trials is limited. In fact, there is only one relatively small randomised study (Kapp 2007) comparing the effect of misoprostol + mifepristone with misoprostol only (Comparison 2). This study demonstrated that the addition of mifepristone in second trimester abortion reduces the induction to abortion interval from 18 hours (95% CI 1 to 22) to 10 hours (95% CI 8 to12), while the occurrence of side-effects in both groups was similar. Indirect evidence, however, suggests a beneficial effect of adding mifepristone to prostaglandin tablets or gel since the induction-to-abortion interval is generally shorter in regimens using mifepristone + prostaglandins (Comparisons 1, 3, 4, 5 and 7) than those using prostaglandins alone (Comparisons 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 and 19). Additionally, mifepristone is known to potentiate the uterine effect of misoprostol and is superior to misoprostol alone in first trimester abortion.

Misoprostol may be administered by different routes, the oral route being the least effective (Comparisons 3, 4 and 5). For regimens using misoprostol, vaginal dosing appears to be the most efficient when compared to both oral and sublingual regimens. Among multiparous women undergoing medical abortion with misoprostol alone, sublingual administration appears equally effective as vaginal administration. No study of second trimester medical abortion has compared vaginal with buccal administration of misoprostol.

The optimal dose of vaginally administered misoprostol is difficult to ascertain since there are no randomised studies comparing various dosing schemes for vaginal administration. Four randomised clinical trials showed that the induction to abortion interval with 3-hourly vaginal administration of prostaglandins was significantly shorter than 6-hourly administration without significant increase in side-effects (Comparisons 15 and 16).

There is insufficient data to make any gestational, age-specific recommendations on the dosage and regimen for abortion. Since the uterus becomes more sensitive to prostaglandins with increasing gestational age, reducing the dosage or frequency of administration should be considered at later gestational ages (Ho 2007). The age range considered in this review includes 12 through 28 weeks of gestation. Overall, from the design of the included studies, there is no indication for confounding by gestational age.

Other considerations for second trimester medical abortion regimens which could not be addressed in this review include the effect on the abortion process of the use of pre-procedure feticide to avoid the occurrence of a fetus with signs of life at abortion, and therapeutic strategies for women who have not aborted after 24 hours of treatment.

There are considerable differences in practices regarding the management of the placenta following the expulsion of the fetus. We considered surgical evacuation any procedure where an instrument was introduced into the uterine cavity. Indications for surgical evacuation include the removal of retained products of the placenta and heavy vaginal bleeding, where reported. Fewer women required surgical evacuation when misoprostol was administrated vaginally when compared to women having mid-trimester abortion by intra-amniotic instillation of $PGF_{2\alpha}$ (OR 0.52, 95% CI 0.31 to 0.87) (Comparison 9). Apart from the latter finding, there were no statistically significant differences in reported frequencies of surgical removal of the placenta among women undergoing misoprostol-induced abortions when compared to other regimens.

Diarrhoea is the most common adverse reaction that has been reported consistently with misoprostol, but it is usually mild and self limiting. Nausea and vomiting may also occur and generally resolves in two to six hours (Tang 2007). Uterine rupture is a rare but serious complication of abortion in the second trimester of pregnancy, especially in women with a previous uterine scar (Berghella 2009). Uterine rupture is uncommon and did not occur during any of the included trials; thus, its relative risk with differing medical regimens are not informed by this review.

Summary of main results

Thirty-six randomised controlled trials were included in the review. The included studies addressed the various agents for pregnancy termination and methods of administration which were grouped into 28 comparisons. When used alone, misoprostol is an effective inductive agent, though it appears to be more effective in combination with mifepristone.

Misoprostol is preferably administered vaginally, although among multiparous women sublingual administration appears equally effective. The optimal dose of vaginally administered misoprostol could not be determined, as no randomised studies could be identified. Low doses of misoprostol are associated with fewer side-effects, while moderate doses are more efficient in completing abortion. Four randomised controlled trials showed that the induction to abortion interval with 3-hourly vaginal administration of prostaglandins is significantly shorter than 6-hourly administration without a significant increase in side-effects.

Many studies reported the need for surgical evacuation in a considerable number of women undergoing mid-trimester termination. Indications for surgical evacuation include the removal of retained products of the placenta and heavy vaginal bleeding. Fewer women required surgical evacuation when misoprostol was administrated vaginally when compared with those having intra-amniotic instillation of PGF_{2a}. Apart from the latter finding, there were no statistically significant differences in reported frequencies of surgical removal of the placenta among women undergoing misoprostol-induced abortions when compared to other regimens. Diarrhoea was more common among women having misoprostol when compared to other agents. However, diarrhoea is reportedly mild and self limiting.

Overall completeness and applicability of evidence

The results of this review fit well into the current practices of mid-trimester termination of pregnancy.

Quality of the evidence

All randomised controlled trials, most of these being unblinded. Given the heterogeneity of the some studies included in the review, the internal validity of the findings is limited.

Potential biases in the review process

None.

Agreements and disagreements with other studies or reviews

Agree with recent Society for Family Planning Guidelines, in press.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review suggest that the most efficient regimen for medical abortion in the second trimester is the combination of mifepristone and misoprostol. If mifepristone is not available, misoprostol alone is a reasonable alternative. The available data suggest that vaginal administration is the most efficient route of administration, and 3-hourly intervals of administration are more effective than 6-hourly intervals. Meta-analysis of the various randomised controlled trials on misoprostol was hampered by the heterogeneity in medical regimens used among the included trials. Included studies indicate that adverse effects of misoprostol are usually mild and dose dependant. Apart from pain resulting from uterine contractions, diarrhoea is the most common side-effect that has been reported consistently with misoprostol. There are considerable differences in practices regarding the management of the placenta following the expulsion of the fetus.

Implications for research

This review highlights the importance of developing a standardised medical method for women requesting mid-trimester abortion. Further research is needed to evaluate the gestational-age-specific dosage of misoprostol for mid-trimester abortion. In addition, more data are needed to guide medical and/or surgical strategies for women with a uterine scar resulting from prior hysterotomy (see Berghella 2009) and for those who failed to abort within 24 hours or five doses of misoprostol. Finally, more research is needed to evaluate the additional value, optimal dose and timing of mifepristone when used in combination with misoprostol.

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None

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Zieman 1997

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CHARACTERISTICS OF STUDIES

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

Akoury 2004

Methods	Computer-generated randomisation sequence with stratification for participating centre and gestational age (≥20 weeks versus < 20 weeks) using blocks of 6. A central office allocated study patients to groups using sealed opaque envelopes. Women were randomly assigned.
Participants	136 pregnant women (group I: 84, group II: 52) Inclusion criteria: singleton, live fetus at 15 to 24 weeks' gestation with a complex fetal anomaly and/or abnormal fetal karyotype were included. Exclusion criteria: allergy to prostaglandins, a previous classic cesarean section or hysterotomy, active bleeding, severe asthma, severe oligohydramnios, pre-labor rupture of membranes.
Interventions	Group I: 400 mg of misoprostol in the posterior fornix of the vagina every 4 hours for a total of 6 doses or until delivery occurred. If after 24 hours no labor commenced, an intravenous solution of oxytocin, 100 U/of L Ringer's lactate at 100 mL per hour, was commenced. Group II: 400 µg misoprostol orally every 4 hours for a total of 6 doses or until delivery occurred. If after 24 hours no labor commenced, an intravenous solution of oxytocin, 100 U/of L Ringer's lactate at 100 mL per hour, was commenced.
Outcomes	Primary outcome: time from the start of the procedure to placental delivery. Secondary outcomes: incidence of major and minor maternal complications, women's views of the method and the success rate for culture of fetal umbilical cord.
Notes	In this study, women were randomly assigned to 1 of 3 groups: intra-amniotic PGF2a, vaginal misoprostol, or oral misoprostol. (n=217). The women receiving PGF2a were excluded from our analyses, because of the use of laminaria. Definition of abortion: expulsion of the fetus and placenta. No clear information was provided regarding the policy of evacuation of the uterus. No major complications occurred.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Armatage 1996

Methods	Patients were randomised into 2 groups using sealed sequentially numbered envelopes.
Participants	99 pregnant women (group I: 50, group II: 49) Inclusion criteria: uncomplicated pregnancies, between 12-20 weeks gestation. Exclusion criteria: multiple pregnancy, known fetal abnormality, significant maternal illness.
Interventions	Group I: gemeprost pessaries at 3-hourly intervals up to a maximum of 5 in 24 hours, until fetal expulsion. Group II: gemeprost pessaries at 6-hourly intervals until fetal expulsion. Where abortion did not occur within 48 hours, an intravenous oxytocin infusion was commenced unless delivery was deemed imminent.
Outcomes	Primary outcome: abortion interval, abortion rates. Secondary outcomes: analgesia, side-effects, surgical evacuations.
Notes	Definition of abortion: expulsion of the fetus. Following delivery of the fetus, intramuscular Syntometrine (ergometrine maleate 500 µg and oxytocin 5 iu, Sandez Products Limited) was given. One women received a blood transfusion (group 1). Women underwent surgical evacuation if the placenta was retained or did not appear intact.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Bartley 2002

Methods	Randomisation was carried out using opaque envelopes. These envelopes were sealed, then shuffled and numbered consecutively in two batches of 50.
Participants	100 pregnant women (group I: 50, group II: 50). Inclusion criteria: gestation 12 to 20 weeks. No exclusion criteria were reported. A history of previous caesarean section was not considered a reason for exclusion. A history of previous caesarean section was not considered a reason for exclusion.
Interventions	All: 200 mg mifepristone and admission followed approximately 36 hours later:

Bartley 2002 *(Continued)*

	Group I: 800 µg misoprostol tablets inserted in the posterior vaginal fornix followed by 400 µg misoprostol tablets orally every 3 hours for a maximum of four doses over the first 24 hours; Group II: 1 mg gemeprost inserted in the posterior vaginal fornix every 6 hours for a maximum of four doses over the first 24 hours. If abortion did not occur within 24 hours, 1 mg vaginal gemeprost was administered every 3 hours to a maximum of five doses over the next 12 hours. If abortion did not occur after this course of gemeprost, the abortion was completed by intravenous oxytocin, repeated course of gemeprost or dilatation and evacuation.
Outcomes	Primary outcome: prostaglandin to abortion interval. Secondary outcomes: differences in percentage of women delivered by 24 hours, incidence in side effects and adverse events.
Notes	No clear definition of abortion. One woman required a blood transfusion and an emergency evacuation of the uterus due to severe haemorrhage.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Bebbington 2002

Methods	Randomization was performed with a series of sequentially numbered opaque envelopes that contained allocations determined through the use of a random number table.
Participants	114 pregnant women (group I: 49, group II: 65) Inclusion criteria: midtrimester abortion. Exclusion criteria: hypersensitivity to prostaglandins, inability to understand English to ensure informed consent.
Interventions	Group I: misoprostol 400 µg in the posterior vaginal fornix every 4 hours. Group II: misoprostol 200 µg orally every hour for 3 hours and then 400 µg orally every 4 hours. If the patient was undelivered after 24 hours, the attending physician determined further management. The options available were to increase the dosage of misoprostol using the same route of administration, to change the route of administration of the misoprostol, to proceed with a high-dose oxytocin infusion, or to proceed with surgical evacuation of the uterus.
Outcomes	Primairy outcomes: induction to abortion interval. Secondary outcomes: maternal fever >38°C; maternal infection defined as maternal fever, elevated white blood cell count, and the need for antibiotics in the postabortion period; maternal side effects

Bebbington 2002 *(Continued)*

	from the medication including nausea or diarrhoea, blood loss, the need for additional operative intervention; and the failure to achieve a medical termination of pregnancy.
Notes	Definition of abortion: expulsion of the fetus. If the placenta remained undelivered after 2h, an attempt was made at manual extraction under general anaesthesia. No major complications reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Behrashi 2008

Methods	Random assignment, not specified.
Participants	60 pregnant women (group I: 30, group II: 30) Inclusion criteria: 14-28 weeks gestation. Exclusion criteria: contraindications to prostaglandin therapy, placenta previa, cervical changes, uncontrolled convulsion, glaucoma, inflammatory bowel disease.
Interventions	Group I: 400 µg misoprostol, vaginally Group II: 400 µg misoprostol, orally These regimens was followed by 400 µg of misoprostol up to 3 doses, if needed. After delivery: 30 unit oxytocin (in 1000 ml Ringer's solution).
Outcomes	Complete expulsion, induction to abortion interval, side-effects, surgical evacuation.
Notes	Definition of abortion: expulsion of fetus and placenta. No major complications occurred. No time interval was given by the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	

Behrashi 2008 *(Continued)*

Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Bhattacharjee 2008

Methods	The patients were randomly allocated into two groups using a computer-generated randomisation protocol. A computer-generated randomisation sequence was used to assign participants into two treatment groups. The allocation was concealed in sealed, sequentially numbered, brown envelopes, which had been prepared by the statistician of each centre and handed over to the respective pharmacy department.
Participants	277 pregnant women (group I: 139, group II: 138) Inclusion criteria: 13 - 20 weeks singleton pregnancy, young healthy women. Exclusion criteria: gestation < 13 or > 20 weeks, contraindication for misoprostol use.
Interventions	Group I: vaginal administration 400 µg misoprostol at the interval of three hours, up to a maximum five doses over 24h. Group II: sublingual administration 400 µg misoprostol, at the interval of three hours, up to a maximum five doses over 24h. The patients were instructed to keep the tablets under the tongue until these were dissolved and not to spit out or swallow the content for at least one hour post-administration. Those women, who failed to abort within 24 h of initiation of the treatment,received a second course of misoprostol, with the same allocated regimen, over a period of another 24 h. If a woman failed to abort after 48 h, the regimen was declared unsuccessful and she was offered a regimen of extra amniotic 0.1% ethacridine lactate infusion (single instillation) or repeated doses of dinoprostone gel (0.5 mg) in the cervical canal six-hourly up to a maximum of three doses.
Outcomes	Primary outcomes: induction to abortion interval, abortion within 24 and 48 hours. Secondary outcomes: blood loss, surgical evacuations, side-effects.
Notes	Definition of abortion: expulsion of fetus and placenta without operative intervention. Exploration of the uterus was performed under deep sedation or short general anaesthesia if the placenta was found to be incompletely expelled. No major complications reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Borgida 1995

Methods	Sequentially numbered, sealed, opaque envelopes containing indicator cards and were opened at enrolment. The randomisation sequence was determined by a random-number table and a block size of 6.
Participants	50 pregnant women (group I: 27, group II: 23) Inclusion criteria: abnormal 14-24 weeks pregnancy, age 18-45 years. Exclusion criteria: allergies to medications, cardiac/pulmonary/renal disease.
Interventions	All: pre-med (25 mg diphenhydramine hydrochloride, 10 mg metoclopramide hydrochloride, 5 mg diphenoxylate hydrochloride, 650 mg acetaminophen) every 4-6 hours + 30 minutes after first dose: Group I: 250 µg IM 15M $PGF_{2\alpha}$ injections every 3 hours; Group II: 20 mg intravaginal PGE_2 every 3 hours. After delivery, all patients received oxytocin 40 U/L, and if the placenta was not delivered within approximally 2 hours or excessive bleeding occurred, a curettage was performed.
Outcomes	Primary outcomes: induction to abortion interval, abortion within 24 hours. Secondary outcomes: surgical evacuation, side-effects.
Notes	Definition of abortion: expulsion of fetus. No major complications reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Chai 2009

Methods	The randomisation was done by computer-generated random numbers and the group assignments were put into sealed, opaque envelopes. The randomisation envelope was opened by the research nurse after recruitment. The investigating team members and the research nurse responsible for recruitment were not aware of the randomisation.
Participants	141 pregnant women (group I: 70, group II: 71) were recruited from the Hong Kong centre and Shanghai centre. Inclusion criteria: healthy women aged 18 or older who requested termination of second trimester pregnancy at 12–20 weeks of gestation and were willing to comply with the schedule of follow-up visits. Exclusion criteria: any contraindications to mifepristone, including adrenal disease or steroid-dependent cancer; any contraindications to misoprostol, including mitral stenosis, glaucoma, sickle cell anaemia, diastolic pressure over 100 mmHg, severe asthma or known allergy to prostaglandin; history or evidence of thrombo-embolism, severe or recurrent liver disease or pruritus of pregnancy; a known

Chai 2009 *(Continued)*

	history of or active medical disease; a history of regular use of prescription drugs; an intrauterine contraceptive device in utero; a haemoglobin level ,100 g/l or abnormal liver or renal function tests; breast-feeding or heavy smoker of more than 20 cigarettes per day.
Interventions	Group I: 200 mg mifepristone and 36–38 h later: 600 µg misoprostol vaginally every 3 h for a maximum of four doses. Group II: 200 mg mifepristone was given orally and 600 µg misoprostol was given vaginally simultaneously, followed by 400 µg vaginal misoprostol every 3 h for a maximum of four doses. The patient was reassessed if abortion had not occurred after 24 h. If there were no signs and symptoms suggestive of imminent abortion, a second course of vaginal misoprostol was given for a maximum of five doses (600 µg for the first dose followed by 400 µg every 3 h for a maximum of four doses). If abortion still did not occur, gemeprost was given to terminate the pregnancy.
Outcomes	Primary outcomes: success rate at 24 h. Secondary outcomes: difference in the induction-to-abortion interval and the frequency of side effects between two groups.
Notes	Definition of abortion: expulsion of fetus. No major complications reported. Six patients from Hong Kong centre (five from the immediate dosing group and one from the conventional dosing group) required suction evacuation of the uterus for retained placenta before discharge from the hospital. All patients from Shanghai centre had dilatation and curettage the day following abortion, as it was the routine practice in that hospital.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

el-Refaey 1993

Methods	Randomisation by sealed envelope selection.
Participants	60 pregnant women (group I: 30, group II: 30) Inclusion criteria: 13-20 weeks gestation. Exclusion criteria: none reported.
Interventions	600mg mifepristone (36-48 hours later followed by): Group I: misoprostol 400 µg orally, every 3 hrs, max 3 doses. If abortion did not occur: two further doses of vaginal gemeprost 1 mg, every 3 hrs; Group II: gemeprost 1 mg pessaries vaginally, every 3 hrs, max 5 doses.

el-Refaey 1993 *(Continued)*

Outcomes	Primary outcome: abortion within 24 hours. Secondary outcomes: surgical evacuation, side-effects.
Notes	Definition of abortion: expulsion of fetus and placenta. No information was provided regarding the policy of evacuation of the uterus. No major complications reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

El-refaey 1995

Methods	Randomisation using computer-generated random number tables. A series of numbered, sealed, opaque envelopes was prepared containing allocation.
Participants	69 pregnant women (group I: 34, group II: 35) Inclusion criteria: 13-20 weeks gestation. Exclusion criteria: none reported.
Interventions	All: mifepristone 600 µg orally + vaginal misoprostol 600 µg (first dose) Group I: oral misoprostol 400 µg every 3 hours, max 5d; Group II: vaginal misoprostol 400 µg every 3 hours, max 5d. If after the fifth dose, abortion had not occurred, 1 mg gemeprost was administered the next morning.
Outcomes	Primary outcomes: induction to abortion interval, abortion within 24 hours. Secondary outcomes: side-effects.
Notes	Definition of abortion: abortion occurring after the fifth dose. One patient suffered from rigours, vomiting and eruption of a maculopapular rash following the administration of 600 µg misoprostol. If the placenta was retained, the uterus was surgically evacuated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate

El-refaey 1995 *(Continued)*

Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Faktor 1988

Methods	Randomisation. Authors report that there was 'no selection bias in the choice of the patients'.
Participants	77 pregnant women (group Ia: 35, group Ib: 17, group II: 16, group III: 9) Inclusion criteria: mid-trimester abortion (15-26 weeks gestation). Exclusion criteria: none given.
Interventions	Group Ia: 1.0g oxytetracycline hydrochloride, dissolved in 16-20 ml of normal physiological saline, intra-amniotic. Patients received oxytocin i.v. in increasing dosage after the appearance of uterine contractions un till time of abortion. Group Ib: 1.0g oxytetracycline hydrochloride, dissolved in 16-20 ml of normal physiological saline, intra-amniotic. No oxytocin was given. Group II: 200 cm3 amniotic fluid was exchanged for 200 cm3 of 20% of hypertonic saline. Group III: 40 mg of $PGF_{2\alpha}$, intra-amniotic. Group I is considered as the intervention group and group II and III are considered control groups.
Outcomes	Abortion interval, side-effects.
Notes	Definition of abortion: expulsion of the fetus. After expulsion of the fetus, all patients underwent revision of the uterine cavity under general anaesthesia. No major complications described. For our analysis, we did not include oxytetracycline hydrochloride.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Unclear risk	No baseline characteristics of the separate groups were provided.

Hamoda 2005

Methods	Randomisatin by opening consecutive sealed opaque envelopes generated using random number tables.

Hamoda 2005 *(Continued)*

Participants	69 pregnant women (group I: 32, group II: 37) Inclusion criteria: singleton intrauterine pregnancy, 13-20 weeks gestation. Exclusion criteria: < 16 years, severe asthma, haemorrhagic disorders, treatment with anticoagulants, known allergy to prostaglandins, history of cardiac disease, smoking over the age of 35 years with ECG abnormalities, breast feeding.
Interventions	All: mifepristone 200mg followed 36-48 hours later by: Group I: misoprostol 600 µg sublingually and misoprostol 400 µg sublingually every 3h; Group II: misoprostol 800 µg vaginally and misoprostol 400mg µg vaginally every 3h.
Outcomes	Primary outcome: induction to abortion interval. Secondary outcomes: acceptability of the route of misoprostol administration to the women and staff, side-effects.
Notes	Definition of abortion: not specified. Surgical evacuation was offered to women if the placenta was not delivered within 1h of delivery of the fetus. Two women suffered from heavy bleeding during the abortion and needed a surgical evacuation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Herabutya 2005

Methods	Random allocation by computer generated numbers. The assignments were put into sealed envelopes, which were opened when the women were recruited.
Participants	279 pregnant women (group I: 140, group II: 139) Inclusion criteria: 14-26 weeks gestation (abortion was not offered > 22 weeks apart from lethal fetal conditions). Exclusion criteria: unstable cardiac disease, recent severe asthmatic attack, severe hepatic or renal impairment, ruptured membranes.
Interventions	All: 600 µg misoprostol vaginally Group I: every 6 hrs, max 9 d; Group II: every 12 hrs, max 5 d.
Outcomes	Primary outcome: induction to abortion interval, abortion within 24 hours.

Herabutya 2005 *(Continued)*

	Secondary outcomes: side-effects.
Notes	Definition of abortion: expulsion of fetus. If the placenta was incomplete or failed to be expelled after 1h, an evacuation of the uterus was carried out under general anaesthesia. No major complications reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Ho 1996

Methods	Randomisation schedule was prepared as described by Meinert. Sealed envelopes with serial numbers on the front and containing the group to which the woman was randomised were opened at recruitment.
Participants	50 pregnant women (group I: 25, group II: 25) Inclusion criteria: 14-20 weeks gestation. Exclusion criteria: regular use of prescription drugs, IUD in utero, nursing mothers, multiple pregnancies, heavy smokers.
Interventions	All: 200mg mifepristone orally (36-48 hours later): Group I: 400 µg misoprostol orally, every 3 h, max 5 doses; Group II: 1mg gemeprost vaginally, every 6 hours, max 4 doses. The patient was reassessed after 24h. If there were no signs or symptoms suggestive of imminent abortion, the pregnancy was terminated with 1 mg gemeprost every 3 hours.
Outcomes	Primary outcome: induction of abortion interval, abortion within 24 hours. Secondary outcomes: side-effects, uterine contractions, blood pressure, pulse rate.
Notes	Definition of abortion: not specified. If the placenta was incomplete, an evacuation of the uterus was carried out. No major complications reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate

Ho 1996 *(Continued)*

Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and gravidity.

Ho 1997

Methods	Randomisation schedule as described by Meinert. Schedules were unknown to both patient and clinicans.
Participants	98 pregnant women (group I: 49, group II: 49) Inclusion criteria: good general health, age 16-35 years, singleton pregnancy, 14-20 weeks gestation. Exclusion criteria: past or present ill health, nursing mothers, IUD, smoking >10 cigarettes/day.
Interventions	All: mifepristone 200 mg 36-48 hours later: Group I: misoprostol 200 µg orally, and a placebo vaginally every 3 hours, max 5 doses; Group II: misoprostol 200 µg vaginally, and a placebo orally, every 3 hours, max 5 doses.
Outcomes	Primary outcome: induction of abortion, abortion within 24 hours. Secondary outcomes: side-effects, uterine contractions, blood pressure, pulse rate.
Notes	Definition of abortion: expulsion of fetus. If the placenta was incomplete or failed to be expelled after 1/2h, an evacuation of the uterus was carried out. No major complications reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	Low risk	Blinding of participants and clinicians.
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Inan 1997

Methods	Randomly assigned.
Participants	78 pregnant women (group I: 48, group II: 30) Inclusion criteria: 13-24 weeks gestation, Bishop score <4. Exclusion criteria: none described.

Inan 1997 *(Continued)*

Interventions	Group I: extra-amniotic ethacridine lactate (Rivanol). A No 16 Foley catheter was placed into the uterus. Following inflammation of the balloon of the catheter to 20-30 ml, an average of 10 ml of 0.1 % sterile ethacridine lactate solution per gestational week was instilled extra-amniotically. The catheter was left in place for 24 hours, if not expelled earlier. Group II: 2.5 ml gel containing 0.5 mg PGE2, intracervical (Cerviprost 0.5 mg gel Organon). Group III: extra-amniotic ethacridine lactate combined with oxytocin infusion. 10-20 units/5% DW IV oxytocin induction was started within 2-4 hours following the ethacridine lactate instillation. For analyses, we did not include group III.
Outcomes	Successful abortion rates, side-effects.
Notes	Definition of abortion: Complete evacuation of fetus and placental tissues from the uterus within 24 hours. No major complications described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Kapp 2007

Methods	Sequentially distributed study number in an allocation ratio of 1:1. The randomisation scheme used permuted blocks of eight, selected by a random number generator created using SAS V.9.3. The pharmacy dispensed the study medication.
Participants	64 pregnant women (group I: 32, group II: 32) Inclusion criteria: 18-23 weeks of gestation. Exclusion criteria: known allergy to mifepristone/misoprostol/prostaglandins, preexisting intrauterine fetal demise, premature preterm rupture of membranes, IUD in place, history of chronic adrenal failure, porphyrias, concurrent long term corticosteroid treatment.
Interventions	All: intra-amniotic injection of 1.5 mg digoxin, then: Group I: 200 mg mifepristone, 20–24 hours after study capsule: misoprostol induction using 400 µg misoprostol, followed by 200 µg every 6h (buccally); Group II: 2 placebo tablets (vitamin C). 20–24 hours after study capsule: misoprostol induction using 400 µg misoprostol, followed by 200 µg every 6h (buccally).
Outcomes	Primary outcome: median interval from first misoprostol dose to fetal expulsion. Secondary outcomes: women delivering within 24 hours, proportion of women with a complete delivery requiring additional

Kapp 2007 *(Continued)*

	treatment for retained placenta, the amount of required pain medication, length of hospital stay, side-effects.
Notes	Definition of abortion: expulsion of fetus. If the placenta was incomplete or failed to be expelled after 4h, an evacuation of the uterus was carried out under general anaesthesia. Heavy bleeding occurred in two women.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	Low risk	Blinding for participants, clinicians, and researchers.
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Kelekci 2006

Methods	Patients were randomised to one of four treatment groups by a series of computer-generated random numbers.
Participants	178 pregnant women (group I: 93, group II: 85) Inclusion criteria: genetic indications, 13-24 weeks gestation. Exclusion criteria: previous uterine scar, pulmonary, hepatic, renal or cardiovascular disease, intrauterine death, vaginal bleeding, uterine contractions, any signs of cervical dilatation, a Bishop score of 4, vaginal infection, a discrepancy of 2 weeks between the gestational age determined by last menstrual period and ultrasonographic gestational age
Interventions	Group I: 200 µg misoprostol, vaginally, followed by 100 µg of oral misoprostol every 4 hour for 24 hrs. Group II: extra-amniotic ethacridine lactate, 10 ml instilled per gestational week, to a maximum of 200 ml. Group III: combination of misoprostol and oxytocin. 200 µg misoprostol, vaginally, followed by 100 µg of oral misoprostol every 4 hour for 24 hrs. An initial dose of 6 mU/min oxytocin was given, followed by additional 6 mU/min doses every 20 min. Group IV: combination of ethacridine lactate and oxytocin. Ethacridine lactate was given extra-amniotic, 10 ml instilled per gestational week, to a maximum of 200 ml. Oxytocin was administered in a similar way as in group III. For analyses, we did not include group III and IV.
Outcomes	Time to induce abortion, success/failure rates, side-effects and complications.
Notes	Definition of abortion: complete evacuation of fetal and placental tissues within 24 h of the initiation of medical abortion. 14 cases of endometritis and 20 cases of incomplete abortions were described.

Kelekci 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	B -unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Makhlouf 2003

Methods	First 90 patient were randomly assigned into three groups (see notes). Randomisation of the remainig 40 patients involved the group using misoprostol and glyceryl trinitrate only, because of shortage of finance to buy more prostaglandin tablets. Randomisation involved computer-generated random tables.
Participants	80 pregnant women (group I: 50, group II: 30) Inclusion criteria: 13-28 weeks gestation, Bishop score ≤ 4. Exclusion criteria: contra-indication to induction of abortion by medical methods, e.g. placenta previa, preterm rupture of membranes (PROM) and transverse lie, grand-multiparous women (parity ≥ 5), previous scarred uterus or contra-indications to the drugs.
Interventions	Group I: 100 µg misoprostol, vaginally every 4 hours, with a maximum dose of 500 µg (five doses). Group II: 6 mg prostaglandin E2 , vaginally every 6 hours, with a maximum of 24 mg (four doses). Women with a method failure and a Bishop score ≤ 4 or absence of uterine activity continued abortion by using a Foley's catheter. If uterine contractions started or the Bishop score was > 4, but expulsion did not occur after 24 hours of after expulsion of the Foley catheter, intravenous 5mIU/min of oxytocin infusion was used. We excluded the outcome 'induction to abortion interval' because of this method after 24 hour.
Outcomes	Induction to abortion interval, abortion within 24 hours, side-effects.
Notes	Definition of method failure: absence of fetal expulsion of absence of signs of impending expulsion (regular uterine contractions and cervical dilatation) at the end of 24 hours. No clear information was provided regarding the policy of evacuation of the uterus. No major complications described. Study included 130 pregnant women into three groups. The third group (n = 50) were randomised for the use of nitric oxide donor (glyceryl trinitrate) tablets. Women received 500 µg of glyceryl trimitrate evert 6h, with a maximum of 5 doses. For this review, this group was excluded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	

Makhlouf 2003 *(Continued)*

Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Mehta 1975 a

Methods	Prepared envelopes indicating one of the methods were picked up serially; the investigators being blind to what the envelopes contained till they opened them.
Participants	67 pregnant women (group I: 33, group II: 34) Inclusion criteria: 15-20 weeks gestation. Exclusion criteria: none given.
Interventions	Group I: 20% hypertonic saline, 200 ml. Group II: single dose, 50mg $PGF_{2\alpha}$.
Outcomes	Abortion rates, side-effects.
Notes	Definition of abortion: when complete (spontaneous evacuation of all products of conception) or incomplete abortion (total or partial retainment of placenta or membranes) occurred within 72 hours. No information was provided regarding the policy of evacuation of the uterus. One women in the single dose $PGF_{2\alpha}$ group received a blood transfusion.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Mehta 1975 b

Methods	Prepared envelopes indicating one of the methods were picked up serially; the investigators being blind to what the envelopes contained till they opened them.
Participants	66 pregnant women (group I: 33, group II: 33) Inclusion criteria: 15-20 weeks gestation. Exclusion criteria: none given.
Interventions	Group I: 20% hypertonic saline, 200 ml. Group II: multiple doses of 25mg $PGF_{2\alpha}$, given at 0 hours and 6 hours. Similar doses were instilled at 24 hours and 30 hours when necessary.

Mehta 1975 b *(Continued)*

Outcomes	Abortion rates, side-effects.
Notes	Definition of abortion: when complete (spontaneous evacuation of all products of conception) or incomplete abortion (total or partial retainment of placenta or membranes) occurred within 72 hours. No information was provided regarding the policy of evacuation of the uterus. One women in the single dose $PGF_{2\alpha}$ group received a blood transfusion.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Muzsnai 1979 a

Methods	Random assignment.
Participants	100 pregnant women (group I: 50, group II: 50) Inclusion criteria: 16-24 weeks of gestation. Exclusion criteria: history of uterine surgery.
Interventions	Group I: $PGF_{2\alpha}$ (20mg) + 100 mL 5% NaCl (5g), intra-amniotic. No amniotic fluid removed. Group II: $PGF_{2\alpha}$ (20mg) + 100 mL 10% NaCl (10g), intra-amniotic. No amniotic fluid removed. All patients received i.v. oxytocin stimulation 40 mU/min.
Outcomes	Instillation to abortion time, abortion interval, complications, side-effects.
Notes	Definition of abortion: none given. Incomplete abortion: if placenta was not expelled within 2h after delivery of the fetus, of if haemorrhage occurred. Failure of abortion: if fetus was not expelled within 48h. The procedure was then repeated. Instillation abortion interval: time from amniocentesis to expulsion of fetus. No major complications described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	B - unclear
Blinding?	High risk	

Muzsnai 1979 a *(Continued)*

All outcomes		
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Muzsnai 1979 b

Methods	Random assignment. After completion of 50 patients in group I and II, the remaining patients were assigned to group II, because of favourable outcome.
Participants	130 pregnant women (group I: 50, group II:80) Inclusion criteria: 16-24 weeks of gestation. Exclusion criteria: history of uterine surgery.
Interventions	Group I: $PGF_{2\alpha}$ (20mg) + 100 mL 5% NaCl (5g), intra-amniotic. No amniotic fluid removed. Group II: $PGF_{2\alpha}$ (20mg) + 100 mL 10% NaCl (10g), intra-amniotic. 100mL amniotic fluid removed. All patients received i.v. oxytocin stimulation 40 mU/min.
Outcomes	Instillation to abortion time, abortion interval, complications, side-effects.
Notes	Definition of abortion: none given. Incomplete abortion: if placenta was not expelled within 2h after delivery of the fetus, of if haemorrhage occurred. Failure of abortion: if fetus was not expelled within 48h. The procedure was then repeated. Instillation abortion interval: time from amniocentesis to expulsion of fetus. No major complications described.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Muzsnai 1979 c

Methods	Random assignment. After completion of 50 patients in group I and II, the remaining patients were assigned to group I, because of favourable outcome.
Participants	255 pregnant women (group I: 205, group II: 50) Inclusion criteria: 16-24 weeks of gestation.

Muzsnai 1979 c *(Continued)*

	Exclusion criteria: history of uterine surgery.
Interventions	Group I: $PGF_{2\alpha}$ (20mg) + 25 mL 20% NaCl (5g), intra-amniotic. All amniotic fluid removed. Group II: $PGF_{2\alpha}$ (20mg) + 100 mL 10% NaCl (10g), intra-amniotic. No amniotic fluid removed. All patients received i.v. oxytocin stimulation 40 mU/min.
Outcomes	Instillation to abortion time, abortion interval, complications, side-effects.
Notes	Definition of abortion: none given. Incomplete abortion: if placenta was not expelled within 2h after delivery of the fetus, of if haemorrhage occurred. Failure of abortion: if fetus was not expelled within 48h. The procedure was then repeated. Instillation abortion interval: time from amniocentesis to expulsion of fetus. No major complications described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Muzsnai 1979 d

Methods	Random assignment. After completion of 50 patients in group I and II, the remaining patients were assigned to both groups, because of favourable outcome.
Participants	285 pregnant women (group I: 205, group II: 80) Inclusion criteria: 16-24 weeks of gestation. Exclusion criteria: history of uterine surgery.
Interventions	Group I: $PGF_{2\alpha}$ (20mg) + 25 mL 20% NaCl (5g), intra-amniotic. All amniotic fluid removed. Group II: $PGF_{2\alpha}$ (20mg) + 100 mL 10% NaCl (10g), intra-amniotic. 100mL amniotic fluid removed. All patients received i.v. oxytocin stimulation 40 mU/min.
Outcomes	Instillation to abortion time, abortion interval, complications, side-effects.
Notes	Definition of abortion: none given. Incomplete abortion: if placenta was not expelled within 2h after delivery of the fetus, of if haemorrhage occurred. Failure of abortion: if fetus was not expelled within 48h. The procedure was then repeated.

Muzsnai 1979 d *(Continued)*

	Instillation abortion interval: time from amniocentesis to expulsion of fetus. No major complications described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Ngai 2000

Methods	Randomisation schedule as described by Meinert. Sealed envelopes with serial numbers were prepared. At enrolment, a serial number was given according to the sequence of entry.
Participants	139 pregnant women (group I: 70, group II: 69) Inclusion criteria: healthy women between 16-35 years, 14-20 weeks gestation. Exclusion criteria: regular use of prescription drugs, IUD in utero, nursing mothers, multiple pregnancies, heavy smokers.
Interventions	All: 200mg mifepristone + (36 - 48 h later): Group I: 400 µg misoprostol oral and a vaginal placebo (vitamin B6) every 3 hours; Group II: 200 µg misoprostol vaginally and an oral placebo (vitamin B6) every 3 hours.
Outcomes	Primary outcome: abortion within 24 hours. Secondary outcomes: induction to abortion interval, side-effects.
Notes	Definition of abortion: not specified. If the placenta was incomplete, an evacuation of the uterus was carried out under general anaesthesia. No major complications occurred.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	Low risk	Blinding for participants.
Free of other bias?	Unclear risk	No statistically significant differences between the groups in terms of maternal age and gestational age.

Nielsen 1975

Methods	Randomisation.
Participants	32 pregnant women (group I: 16, group II: 16) Inclusion criteria: gestation more than 14 weeks. Exclusion criteria: none reported.
Interventions	Group I: suprapublical/transvaginal injection of 20% saline, preceded by removal of 50 mL of amniotic fluid. Amount of saline depending on gestation; 14th week 75 mL, 15th week 100 mL, >16th week 150 mL. Group II: suprapublical/transvaginal injection of 40 mg of $PGF_{2\alpha}$, preceded by removal of 50 mL of amniotic fluid. Both groups received an 10 IU/h oxytocin drip (100IU in one litre of 5% glucose) within half an hour. If abortion did not occur before 200IU oxytocin was given, the infusion was stopped for 6-8h and then restarted. PG/saline injection was not repeated.
Outcomes	Abortion interval, complications, side-effects.
Notes	Definition of abortion: none given. Curettage was performed in cases which were considered incomplete. No major complications described.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No apparant differences between the groups in terms of maternal age, gestational age and parity.

Nuutila 1997 a

Methods	Randomisation was done using random numbers tables into three groups. A series of numbered, sealed envelopes were prepared containing the allocation.
Participants	55 pregnant women (group I: 27, group II: 28) Inclusion criteria: 12-24 weeks gestation, singleton pregnancies. Exclusion criteria: none reported.
Interventions	Group I: 100 µg misoprostol vaginally, every 6 hours, max max 6 doses. Group II: 1 mg gemeprost vaginally, every 3 hours, max 8 doses.
Outcomes	Primary outcome: induction to abortion interval.

Nuutila 1997 a *(Continued)*

	Secondary outcomes: side-effects.
Notes	Definition of abortion: expulsion of fetus and placenta. Within 1h after the passage of the fetus, whether or not the placenta was passed, an evacuation of the uterus was carried out under general anaesthesia. No major complications occurred.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Nuutila 1997 b

Methods	Randomisation was done using random numbers tables into three groups. A series of numbered, sealed envelopes were prepared containing the allocation.
Participants	54 pregnant women (group I: 26, group II: 28) Inclusion criteria: 12-24 weeks gestation, singleton pregnancies. Exclusion criteria: none reported.
Interventions	Group I: 200 µg misoprostol vaginally, every 12 hours, max 3 doses. Group II: 1 mg gemeprost vaginally, every 3 hours, max 8 doses.
Outcomes	Primary outcome: induction to abortion interval. Secondary outcomes: side-effects.
Notes	Definition of abortion: expulsion of fetus and placenta. Within 1h after the passage of the fetus, whether or not the placenta was passed, an evacuation of the uterus was carried out under general anaesthesia. No major complications occurred.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	

Nuutila 1997 b *(Continued)*

Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Nuutila 1997 c

Methods	Randomisation was done using random numbers tables into three groups. A series of numbered, sealed envelopes were prepared containing the allocation.
Participants	53 pregnant women (group I: 27, group II: 26) Inclusion criteria: 12-24 weeks gestation, singletone pregnancies. Exclusion criteria: none reported.
Interventions	Group I: 100 µg misoprostol vaginally, every 6 hours, max 6 doses. Group II: 200 µg misoprostol vaginally, every 12 hours, max 3 doses.
Outcomes	Primary outcome: induction to abortion interval. Secondary outcomes: side-effects.
Notes	Definition of abortion: expulsion of fetus and placenta. Within 1h after the passage of the fetus, whether or not the placenta was passed, an evacuation of the uterus was carried out under general anaesthesia. No major complications occurred.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Olund 1978

Methods	Randomly assigned.
Participants	92 pregnant women (group I: 23, group II: 23, group III: 23, group IV: 23) Inclusion criteria: 13-25 weeks gestation. Exclusion criteria: none described.
Interventions	Group I: extra-amniotic instillation of 0.1% solution of rivanol, 10 ml per gestational week. Maximum of 150 ml.

Olund 1978 *(Continued)*

	Group II: extra-amniotic instillation of 1 ml of saline containing 0.25 mg $PGF_{2\alpha}$ per ml, 3 ml every 2 hours for up to 24 hours. At a gestational age >16 weeks, the dose was doubled. Group III: Rivanol + $PGF_{2\alpha}$, as in group I and II. Group IV: Rivanol + a half dose of $PGF_{2\alpha}$, as in group III, except for a half dose of $PGF_{2\alpha}$. NB: For our analysis, we included group I and II.
Outcomes	Abortion time, abortion interval, side-effects.
Notes	No definition of abortion was given. No major complications described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Ozerkan 2009

Methods	Randomisation by computer-generated number lists to two groups of 30.
Participants	60 pregnant women (group I: 30, group II: 30) Inclusion criteria: 13-24 weeks gestation. Exclusion criteria: none reported.
Interventions	Group I: 400 µg of misoprostol, vaginally, with an additional 200 µg at two-hour intervals up to five doses. Group II: 600 µg of misoprostol, vaginally, with an additional 400µg at four-hour intervals up to two doses. Patients in either group received a maximum total dose of 1400g of misoprostol. The next dose was skipped whenever there were effective uterine contractions. If the procedure failed on the first day, it was undertaken the next day using the same protocol. Another method of termination was called in case the procedure failed on two consecutive days.
Outcomes	Primary outcome: success rates, time to termination, blood loss, complications, side-effects and cervical features defined ultrasonographically.
Notes	Definition of abortion: expulsion of fetus. Post-abortion curettage of the uterine cavity. No major complications reported.

Risk of bias

Ozerkan 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age and gestational age.

Pongsatha 2008

Methods	Randomisation through block randomisation by the authors.
Participants	148 pregnant women (group I: 72, group II: 76) Inclusion criteria: second trimester abortion, live fetuses, closed/uneffaced cervix without labor. Exclusion criteria: previous uterine scar, hypersensitivity to prostaglandins.
Interventions	Group I: 400 mg misoprostol tablet insertion, every 3h. Group II: 400 mg misoprostol gel insertion, every 3h.
Outcomes	Primary outcome: abortion within 24 hours. Secondary outcomes: side-effects.
Notes	Misoprostol in gel form: mixing misoprostol with 3 mL 1% carboxy methyl cellulose. Definition of abortion: expulsion of fetus. No information was provided regarding the policy of evacuation of the uterus. No major complications reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Sorensen 1984

Methods	Use of random numbers.
Participants	39 pregnant women (group I: 20, group II: 19) Inclusion criteria:13-24 weeks of gestation.

Sorensen 1984 *(Continued)*

	Exclusion criteria: intra-uterine fetal death, cardiopulmonary disease, nephropathy, liver diseases, previous operation on the uterus
Interventions	Group I: 2x PGE2 0.75 mg within 5 hours intracervical/extra amniotic, 5 hours, later followed by oxytocin infusion 0.15 IU/min if no contractions. Group II: $PGF_{2\alpha}$ 40 mg intra-amniotically 5 hours later followed by oxytocin drip 0.15 IU/min if no contractions.
Outcomes	Primary outcomes: abortion success rate, induction-abortion interval. Secondary outcomes: side-effects.
Notes	Definition of abortion: expulsion of fetus. If the placenta was not expelled within 2 hours, an evacuation of the uterus was performed. No major complications reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Steyn 1993

Methods	Randomisation using the balanced block method. Instructions were placed in sealed envelopes.
Participants	20 pregnant women (group I: 10, group II: 10) Inclusion criteria: 14-26 weeks of gestation. Exclusion criteria: fetal death on admission, previous uterine scars, history of asthma, active vaginal or intra-uterine infection, anhydramnios.
Interventions	Group I: 1.5 mg prostaglandin E2 (PGE2) gel extra-amniotically. Group II: 25 mg prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) intra-amniotically. Patients in both groups received oxytocin to a maximum dosage of 120 mU per minute if they had not aborted 18 hours after the original administration of either prostaglandin regimen. If the patient had not aborted within 36h, the method was regarded unsuccessful and the managing physician was free to change the management of choice.
Outcomes	Primary outcome: induction to abortion interval. Secondary outcomes: complications, side effects. Proportion of successful inductions and complications.
Notes	Definition of abortion: none given.

Steyn 1993 *(Continued)*

	No information was provided regarding the policy of evacuation of the uterus. No major complications reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Su 2005

Methods	Random allocation; computer-generated schedule randomisation; numbered, sealed, opaque envelope; envelopes were drawn in consecutive order.
Participants	125 pregnant women (group I: 61, group II: 64) Inclusion criteria: 12-24 weeks gestation. Exclusion criteria: multiple pregnancies, ≥ 2 previous cesarean sections, missed abortion, oligohydramnios, severe asthma, allergy to prostaglandins.
Interventions	Group I: vaginal misoprostol 400 µg /3h, max 5d in 24 hrs. Group II: intra amniotic PGF2α 1,5mg, max 5d in 24 hrs.
Outcomes	Primary outcome: induction to abortion interval. Secondary outcomes: abortion within 24 and 48 hours, the need for repeat course of medications, evacuation of uterus, adverse effects.
Notes	Definition of abortion: expulsion of the fetus. Evacuation of the uterus was not performed routinely. No major complications reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Tang 2004

Methods	Computer-generated random numbers; sealed envelopes, opened at recruitment.
Participants	220 pregnant women (group I: 112, group II: 108) Inclusion criteria: 12-20 weeks gestation. Exclusion criteria: regular use of prescription drugs, IUD in utero, nursing mothers, multiple pregnancies, heavy smokers.
Interventions	Group I: Vaginal administration 400 µg misoprostol every 3h, max 5 doses in 24 hours. Group II: Sublingual administration 400 µg misoprostol every 3h, max 5 doses in 24 hours.
Outcomes	Primary outcome: success rate at 48 hours. Secondary outcomes: success rate at 24 hours, side-effects.
Notes	Definition of abortion: expulsion of the fetus and placenta. If the placenta was incomplete, evacuation of the uterus was performed. No major complications occurred.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Tang 2005

Methods	Computer-generated randomisation sequence; sealed, sequentially numbered treatment packs, which were filled and labelled in accordance with the list of randomisation.
Participants	118 women (group I: 58, group II: 60) Inclusion criteria: >18 years, 12-20 weeks gestation. Exclusion criteria: regular use of prescription drugs, IUD in utero, nursing mothers, multiple pregnancies, heavy smokers.
Interventions	all: mifepristone 200mg orally, 36-48h later: Group 1: misoprostol 400 µg sublingual and 2 placebo tablets orally every 3 hrs, max 5 d; Group 2: misoprostol 400 µg orally and 2 placebo tablets sublingually every 3 hrs, max 5 d.
Outcomes	Primary outcome: success rate at 24 h. Secondary outcomes: induction-to-abortion interval, side-effects.
Notes	Definition of abortion: not specified.

Tang 2005 *(Continued)*

	If the placenta was incomplete, evacuation of the uterus was performed. No major complications occurred.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	Low risk	Blinding for participants and clinicians.
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Thong 1996

Methods	Sealed, opaque envelopes containing either of the two treatment groups. These envelopes were shuffled and numbered consecutively.
Participants	100 pregnant women (group I: 50, group II: 50) Inclusion criteria: 12-19 weeks gestation. Exclusion criteria: <16 years.
Interventions	All: 200mg mifepristone, 36 hours later: Group I: 1mg pessary gemeprost vaginally in 6 hour intervals, max 4 doses in 24 hour. After 24 hours without abortion 1 mg gemeprost in 3 hour intervals, max 24 hours; Group II: 0.5mg pessary gemeprost vaginally in 6 hour intervals, max 4 doses in 24 h. After 24 hours 1 mg gemeprost in 3 hour intervals.
Outcomes	Primary outcome: abortion within 24h. Secondary outcomes: side-effects.
Notes	Definition of abortion: expulsion of fetus and placenta. Evacuation of the uterus was carried out if the placenta was not expelled spontaneously or if it was judged to be incomplete. One woman in group II required a blood transfusion of two units because of heavy bleeding in association with a retained placenta after expulsion of the fetus.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	

Thong 1996 *(Continued)*

Free of other bias?	Low risk	No apparent differences between the groups in terms of maternal age, gestational age and parity.

von Hertzen 2009

Methods	A computer-generated randomisation sequence was produced by WHO staff in Geneva to assign participants within each centre to sublingual or vaginal treatment group by randomly permuted blocks with a fixed block size of six. Allocation was concealed by using sealed, opaque, sequentially numbered envelopes, which were filled and labelled in accordance with the list of randomization for each centre by Magistra, Geneva, Switzerland.
Participants	681 pregnant women (group I: 340, group II: 341) Inclusion criteria: healthy, older than the age of legal consent, had a single intrauterine pregnancy of 13–20 weeks (91–140 days) duration as verified by ultrasound and had haemoglobin 100 g/l or higher. Exclusion criteria: any indication of serious past or present illness; an allergy to misoprostol; a habit of heavy smoking (.20 cigarettes/day); a scar in the uterus or cervix or any gynaecological anomaly detected with ultrasound; mitral stenosis, glaucoma or sickle cell anaemia; diastolic blood pressure .90 mmHg; uncontrolled bronchial asthma; systolic blood pressure ,90 mmHg; history or evidence of thromboembolism or liver disease; presence of an intrauterine device; or haemolytic disorders.
Interventions	Group I: 400 µg misoprostol vaginally, 2 placebo tablets sublingually, every 3 hours up to five doses until abortion took place. Group II: 400 µg misoprostol sublingually, 2 placebo tablets vaginally, every 3 hours up to five doses until abortion took place. Placebo tablets were manufactured by Labatec, Geneva, Switzerland; similar shape and colour as misoprostol tablets. The blisters were labelled indicating which tablets were to be taken sublingually and which tablets vaginally. Additional misoprostol tablets were provided to the centres to be used sublingually for those women who did not abort within 24 h. After expulsion of the fetus, one additional dose of the tablets was administered.
Outcomes	Primary outcome: successful abortion (including complete and incomplete abortion) within 24 h. Secondary outcome: successful abortion within 48 h induction-to-abortion interval (the start of treatment to expulsion of fetus, side effects and women's perceptions of the method.
Notes	Definition of abortion: complete or incomplete abortion, while treatment failures included missed abortion, continuing pregnancy and undetermined outcomes. Ten women received a blood transfusion and three women required hospitalization after discharge, two of them for surgical evacuation of the uterus and one for reasons unrelated to the study. After abortion, the products of gestation were examined to see whether the abortion was complete. If necessary, or if it was a local routine practice (three centres), exploration and evacuation of the uterus was performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	Low risk	

von Hertzen 2009 *(Continued)*

Free of other bias?	Low risk	A stratified analysis was conducted by parity because there was a highly significant interaction of treatment by parity. No apparent differences between the groups in terms of maternal age and gestational age.

Waldron 1990

Methods	Randomisation.
Participants	58 pregnant women (group I: 29, group II: 29) Inclusion criteria: 14-20 weeks of gestation. Exclusion criteria: signs or symptoms of spontaneous abortion, known or suspected hypersensitivity to prostaglandins, cardio-pulmonary disease, hypertension, urticaria, eczema, ulcerative colitis, diabetes, epilepsy, renal disease, liver disease.
Interventions	Group I: 1 mg gemeprost in vaginal pessaries, 3h interval, maximum of 5 doses. Group II: 20 mg of $PGF_{2\alpha}$ in 40 ml of 20% NaCl, intra-amniotic. If abortion had not occurred within 24 hours, an alternative treatment was commenced at the discretion of the clinician. Following delivery of the fetus, oxytocin or ergometrine in routine dosages were used at the clinician's discretion, and surgical evacuation of the uterus was performed if the placenta was not delivered within two hours.
Outcomes	Abortion interval, side-effects, complications.
Notes	Definition of abortion: abortion within 24 hours. If the placenta was not expelled within 2 hours, an evacuation of the uterus was performed. No major complications described.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No apparent differences between the groups in terms of maternal age, gestational age and parity.

Webster 1996

Methods	Women were randomly allocated using a series op opaque envelopes that had been prepared by using random number tables.
Participants	70 pregnant women (group I: 35, group II: 35) Inclusion criteria: 13-20 weeks of gestation. Exclusion criteria: none given.

Webster 1996 *(Continued)*

Interventions	Group I: 200 mg mifepristone prior to admission for prostaglandin. A first dose of 800 µg of misoprostol (8.00 am) was given vaginally, followed by 400 µg doses administered orally on a 3h basis, to a maximum of 4 doses. Group II: 600 mg mifepristone prior to admission for prostaglandin. A first dose of 800 µg of misoprostol (8.00 am) was given vaginally, followed by 400 µg doses administered orally on a 3h basis, to a maximum of 4 doses. If abortion had not occured following the final dose of misoprostol, the treatment was considered to be a failure and mifepristone 600 mg was given at midnight, followed by a course of 1 mg gemeprost pessaries at 3h intervals commenced the following morning.
Outcomes	Induction to abortion interval, side effects.
Notes	Complete abortion: on clinical grounds, and then no further interventions were undertaken. Surgical evacuation of the uterus was performed if women did not pass the complete placenta. One woman from each group required a blood transfusion as a result of blood loss at this time.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	Women in the 600 mg group were significantly older than their counterparts in the 200 mg group. No apparent differences between the groups in terms of gestational age and parity.

WHO 1976

Methods	Computer-generated randomisation table. Identity of the compound was kept in a sealed envelope until the patient was accepted for the study.
Participants	1513 pregnant women (group I: 717, group II: 796) Inclusion criteria: 13-22 weeks of gestation. Exclusion criteria: previous heart disease, hypertension, respiratory disease, ulcerative colitis, diabetes mellitus, disorders of blood coagulation, kidney disease, liver disease, sickle-cell anaemia, severe hypersensitivity, serious systemic disease, contraindication to transperitoneal uterine puncture (previous abdominal surgery on the body of the uterus, large uterine myomata/pelvic tumors, major congenital abnormalities of the uterus, rupture of membranes, earlier failed saline induction).
Interventions	Both groups were punctured with a fine-bore needle and a small amount of amniotic fluid withdrawn to confirm the intra-amniotic position. Group I: 200 mL 20% saline was slowly injected, intra-amniotic; Group II: 5 mL tromethamine salt of $PGF_{2\alpha}$ (= 25mg $PGF_{2\alpha}$) was injected, intra-amniotic. A catheter was left in position and 6h later a second injection op 25mg $PGF_{2\alpha}$ was given.
Outcomes	Abortion interval, complications, side-effects.

WHO 1976 *(Continued)*

Notes	Definition of abortion: spontaneous expulsion of placenta through the cervix into the vagina. If the placenta was incomplete, evacuation of the uterus was performed. Re-admission to hospital was necessary for 17 patients given $PGF_{2\alpha}$ and 13 patients given saline (excessive blood loss, retained products of conception, signs of genital tract infection).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No apparant differences between the groups in terms of maternal age, gestational age and parity.

Wong 1998

Methods	Randomisation schedule, (sealed) envelopes bearing the subject number and allocation were prepared as described by Meinert. The envelopes were opened only when recruited.
Participants	140 pregnant women (group I: 70, group II: 70) Inclusion criteria: healthy women, age 16-40 years, 14-20 weeks gestation. Exclusion criteria: regular use of prescription drugs, cardiac disorders, IUD in situ, missed abortion, multiple pregnancy, nursing mothers.
Interventions	Group I: misoprostol 400 µg vaginally every 3 hours, max 5d. Group II: gemeprost 1 mg vaginally every 3 hours, max 5d.
Outcomes	Primary outcomes: induction-abortion interval, rates of successful abortion (within 24 h), complete abortion. Secondary outcomes: side-effects.
Notes	Definition of abortion: expulsion of fetus. If the placenta was incomplete, evacuation of the uterus was performed under general anaesthesia. No major complications reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Wong 2000

Methods	Randomisation schedule, envelopes bearing the subject number and allocation were prepared as described by Meinert. The envelopes were opened only when recruited.
Participants	148 pregnant women (group I: 74, group II: 74) Inclusion criteria: healthy women, 14-20 weeks' gestation. Exclusion criteria: regular use of prescription drugs, IUD in situ, missed abortion, multiple pregnancy, nursing mothers.
Interventions	All: vaginal misoprostol 400 µg Group I: every 3 hours; Group II: every 6 hours.
Outcomes	Primary outcomes: induction to abortion interval, abortion within 24 hours, complete abortion. Secondary outcomes: side-effects.
Notes	Definition of abortion: expulsion of fetus and placenta. If the placenta was incomplete, evacuation of the uterus was performed under general anaesthesia. No major complications reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - adequate
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

Zauva 1989

Methods	Random allocation.
Participants	37 pregnant women (group I: 19, group II: 18) Inclusion criteria: normal physical investigations, 12-20 weeks gestation, regular menstrual cycles, certain last menstrual period. Exclusion criteria: previous Caesarian section, hysterotomy, myomectomy, any other surgery on the uterus.
Interventions	Group I: 150 ml (0.1%) emcredil by extra-amniotic instillation. Group II: 150 ml normal saline.
Outcomes	Induction-abortion interval, side-effects.

Zauva 1989 *(Continued)*

Notes	Definition of abortion: expulsion of the fetus. No major complications described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	B - unclear
Blinding? All outcomes	High risk	
Free of other bias?	Low risk	No statistically significant differences between the groups in terms of maternal age, gestational age and parity.

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

Study	Reason for exclusion
Allahbadia 1992	No randomisation
Ballard 1981	No randomisation
Ben-Meir 2009	Fetal demise > 20%
Caliskan 2005	Fetal demise > 20%
Caliskan 2009	Fetal demise > 20%
Carbonell 2008	Different primary outcomes
Dickinson 1998	Multiple pregnancies, previous uterine scar included
Dickinson 2002	Multiple pregnancies, previous uterine scar, fetal death included
Dickinson 2003	Multiple pregnancies included, previous uterine scar included
Feldman 2003	27% of the women did not meet the inclusion criteria
Frydman 1988	Pre-treatment trial
Ghorab 1998	Fetal demise > 20%, cervix dilatation before treatment
Ghosh 1980	Authors excluded women with incomplete abortion
Gilbert 2001	Simple randomisation
Goswami 1982	No randomisation
Guix 2005	Concealment score: C
Herabutya 2001	Odd and even number randomisation, biased and concealment score C

Study	Reason for exclusion
Hidar 2001	Inclusion of fetal death, premature rupture of membranes
Hill 1991	No randomisation
Ho 1993	Mifepristone pre-treatment trial
Jain 1994	Fetal demise > 20%, live fetuses received a lethal cardiac injection
Jain 1999	Fetal demise included
Jansen 2008	Cervical dilatation
Jarnbert 1999	Cervical ripening
Kamali 1998	No randomisation
Kapp 2007 (2)	Fetal demise > 20%
Klinte 1983	No randomisation
le Roux 2002	Trilostane and danazol as pre-treatments to misoprostol
Manabe 1981	Inclusion of quinine
Munthali 2001	Fetal demise > 20%
Nigam 2006	Simple randomisation
Niromanesh 2005	Concealment allocation: C
Nor Azlin 2006	Cervical dilatation
Nuthalapaty 2005	Use of catheter which was left in place during treatment to promote cervical ripening
Olund 1979	No randomisation
Owen 1996	First dilatation with hygroscopic dilatators and oxytocin infusion
Owen 1999	Women received laminaria for cervical ripening
Perry 1999	Complex and unconventional regime, use of laminaria and cardiac injection
Pulkkinen 1980	No randomisation
Ragab 1976	No primary outcomes could be read off the tables
Ramsey 2004	Cervical dilatation
Shukla 1984	No randomisation
Sørensen 1986	Open list of random numbers
Thong 1993	No randomisation
Thong KJ, Baird 1992	Dilapan laminaria tents, cervical dilatation

Study	Reason for exclusion
Wong 1996	Pre-treatment trial
Yapar 1996	Fetal demise > 20%
Yilmaz 2007	Fetal demise > 20%

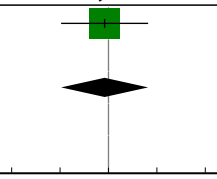
DATA AND ANALYSES

Comparison 1. Comparison: mifepristone+misoprostol versus mifepristone+gemeprost

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-4.89, 4.09]
2 Abortion within 24 hours	3	210	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.23, 2.24]
3 Surgical evacuation	3	209	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.27, 1.35]
4 Pain	3	199	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.19, 1.21]
5 Nausea	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.19, 1.90]
6 Vomiting	2	110	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.47, 2.13]
7 Diarrhoea	2	110	Odds Ratio (M-H, Fixed, 95% CI)	2.09 [0.83, 5.23]

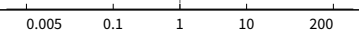
Analysis 1.1. Comparison 1 Comparison: mifepristone+misoprostol versus mifepristone+gemeprost, Outcome 1 Induction to abortion interval.

Study or subgroup	Mifepristone/misoprostol N	Mifepristone/misoprostol Mean(SD)	Mifepristone/gemeprost N	Mifepristone/gemeprost Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ho 1996	25	11.8 (9)	25	12.2 (7.1)		100%	-0.4[-4.89,4.09]
Total ***	**25**		**25**			**100%**	**-0.4[-4.89,4.09]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.17(P=0.86)							



Analysis 1.2. Comparison 1 Comparison: mifepristone+misoprostol versus mifepristone+gemeprost, Outcome 2 Abortion within 24 hours.

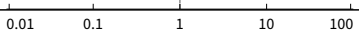
Study or subgroup	Mifepristone/misoprostol n/N	Mifepristone/gemeprost n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bartley 2002	47/50	48/50		40.57%	0.65[0.1,4.09]
el-Refaey 1993	28/30	30/30		34.64%	0.19[0.01,4.06]
Ho 1996	23/25	22/25		24.79%	1.57[0.24,10.3]
Total (95% CI)	**105**	**105**		**100%**	**0.72[0.23,2.24]**
Total events: 98 (Mifepristone/misoprostol), 100 (Mifepristone/gemeprost)					
Heterogeneity: $Tau^2=0$; $Chi^2=1.41$, df=2(P=0.5); $I^2=0\%$					
Test for overall effect: Z=0.57(P=0.57)					



Favours gemeprost — Favours misoprostol

Analysis 1.3. Comparison 1 Comparison: mifepristone+misoprostol versus mifepristone+gemeprost, Outcome 3 Surgical evacuation.

Study or subgroup	Mifepristone/misoprostol n/N	Mifepristone/gemeprost n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bartley 2002	5/50	6/49		35.6%	0.8[0.23,2.8]
el-Refaey 1993	2/30	2/30		12.18%	1[0.13,7.6]
Ho 1996	5/25	10/25		52.22%	0.38[0.11,1.33]
Total (95% CI)	**105**	**104**		**100%**	**0.6[0.27,1.35]**
Total events: 12 (Mifepristone/misoprostol), 18 (Mifepristone/gemeprost)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.97$, df=2(P=0.62); $I^2=0\%$					
Test for overall effect: Z=1.24(P=0.22)					



Favours misoprostol — Favours gemeprost

Analysis 1.4. Comparison 1 Comparison: mifepristone +misoprostol versus mifepristone+gemeprost, Outcome 4 Pain.

Study or subgroup	Mifepristone/misoprostol n/N	Mifepristone/gemeprost n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bartley 2002	44/50	47/49		43.23%	0.31[0.06,1.63]
el-Refaey 1993	14/25	17/25		56.77%	0.6[0.19,1.9]
Ho 1996	25/25	25/25			Not estimable
Total (95% CI)	**100**	**99**		**100%**	**0.47[0.19,1.21]**
Total events: 83 (Mifepristone/misoprostol), 89 (Mifepristone/gemeprost)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.4$, df=1(P=0.53); $I^2=0\%$					
Test for overall effect: Z=1.56(P=0.12)					

Favours misoprostol — Favours gemeprost

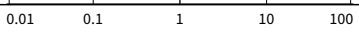
Analysis 1.5. Comparison 1 Comparison: mifepristone +misoprostol versus mifepristone+gemeprost, Outcome 5 Nausea.

Study or subgroup	Mifepristone/misoprostol n/N	Mifepristone/gemeprost n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Ho 1996	8/25	11/25		100%	0.6[0.19,1.9]
Total (95% CI)	**25**	**25**		**100%**	**0.6[0.19,1.9]**
Total events: 8 (Mifepristone/misoprostol), 11 (Mifepristone/gemeprost)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.87(P=0.38)					

Favours misoprostol — Favours gemeprost

Analysis 1.6. Comparison 1 Comparison: mifepristone +misoprostol versus mifepristone+gemeprost, Outcome 6 Vomiting.

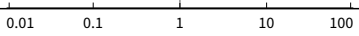
Study or subgroup	Mifepristone/misoprostol n/N	Mifepristone/gemeprost n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
el-Refaey 1993	11/30	13/30		60.93%	0.76[0.27,2.13]
Ho 1996	13/25	11/25		39.07%	1.38[0.45,4.2]
Total (95% CI)	**55**	**55**		**100%**	**1[0.47,2.13]**
Total events: 24 (Mifepristone/misoprostol), 24 (Mifepristone/gemeprost)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.6$, df=1(P=0.44); $I^2=0\%$					
Test for overall effect: Z=0(P=1)					



Favours misoprostol — Favours gemeprost

Analysis 1.7. Comparison 1 Comparison: mifepristone +misoprostol versus mifepristone+gemeprost, Outcome 7 Diarrhoea.

Study or subgroup	Mifepristone/misoprostol n/N	Mifepristone/gemeprost n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
el-Refaey 1993	6/30	2/30		24.84%	3.5[0.65,18.98]
Ho 1996	14/25	11/25		75.16%	1.62[0.53,4.95]
Total (95% CI)	**55**	**55**		**100%**	**2.09[0.83,5.23]**
Total events: 20 (Mifepristone/misoprostol), 13 (Mifepristone/gemeprost)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.56$, df=1(P=0.46); $I^2=0\%$					
Test for overall effect: Z=1.57(P=0.12)					



Favours misoprostol — Favours gemeprost

Comparison 2. Comparison: mifepristone+misoprostol versus placebo+misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abortion within 24 hours	1	64	Odds Ratio (M-H, Fixed, 95% CI)	12.13 [1.43, 102.61]
2 Surgical evacuation	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.02, 2.14]
3 Pain	1	64	Odds Ratio (M-H, Fixed, 95% CI)	1.94 [0.70, 5.38]
4 Nausea	1	64	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.48, 3.44]
5 Vomiting	1	64	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.42, 3.07]

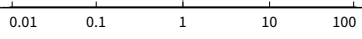
Analysis 2.1. Comparison 2 Comparison: mifepristone+misoprostol versus placebo+misoprostol, Outcome 1 Abortion within 24 hours.

Study or subgroup	Mifepristone n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Kapp 2007	31/32	23/32		100%	12.13[1.43,102.61]
Total (95% CI)	**32**	**32**		**100%**	**12.13[1.43,102.61]**
Total events: 31 (Mifepristone), 23 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.29(P=0.02)					

Favours placebo — Favours mifepristone

Analysis 2.2. Comparison 2 Comparison: mifepristone+misoprostol versus placebo+misoprostol, Outcome 2 Surgical evacuation.

Study or subgroup	Mifepristone n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Kapp 2007	1/32	4/32		100%	0.23[0.02,2.14]
Total (95% CI)	**32**	**32**		**100%**	**0.23[0.02,2.14]**
Total events: 1 (Mifepristone), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					

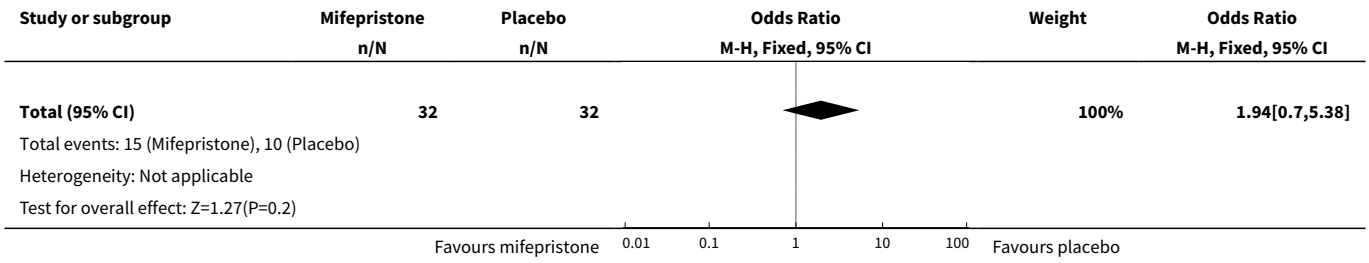


Favours mifepristone — Favours placebo

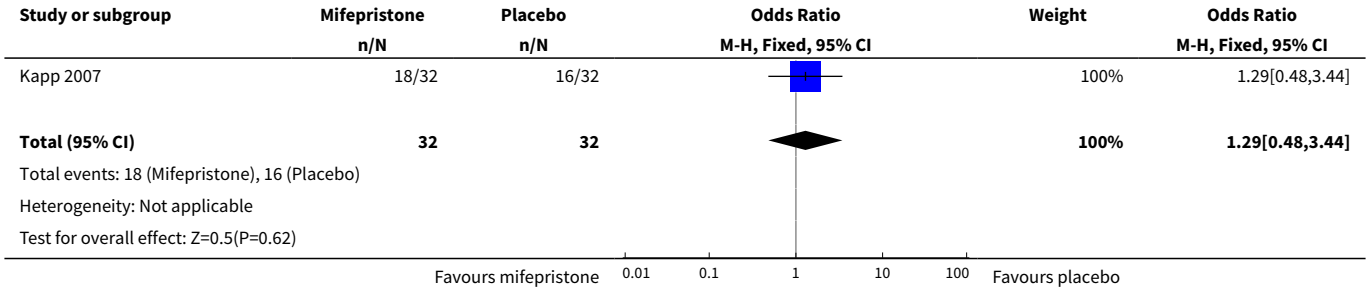
Analysis 2.3. Comparison 2 Comparison: mifepristone+misoprostol versus placebo+misoprostol, Outcome 3 Pain.

Study or subgroup	Mifepristone n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Kapp 2007	15/32	10/32		100%	1.94[0.7,5.38]

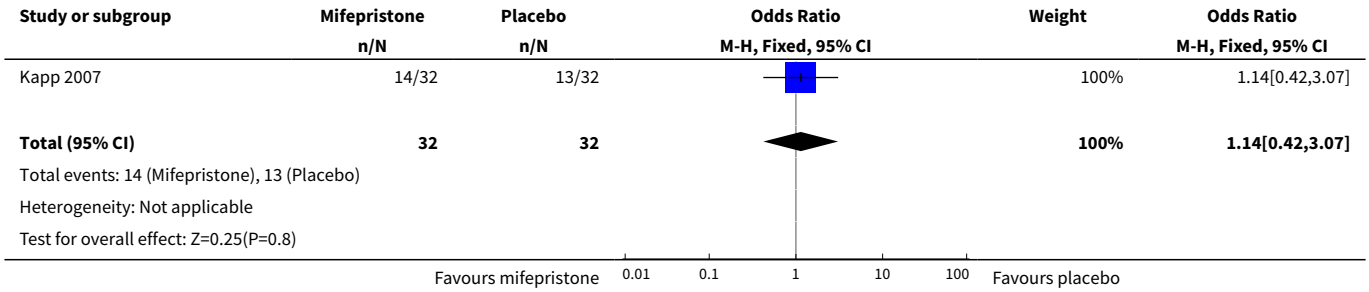
Favours mifepristone — Favours placebo



Analysis 2.4. Comparison 2 Comparison: mifepristone +misoprostol versus placebo+misoprostol, Outcome 4 Nausea.



Analysis 2.5. Comparison 2 Comparison: mifepristone +misoprostol versus placebo+misoprostol, Outcome 5 Vomiting.



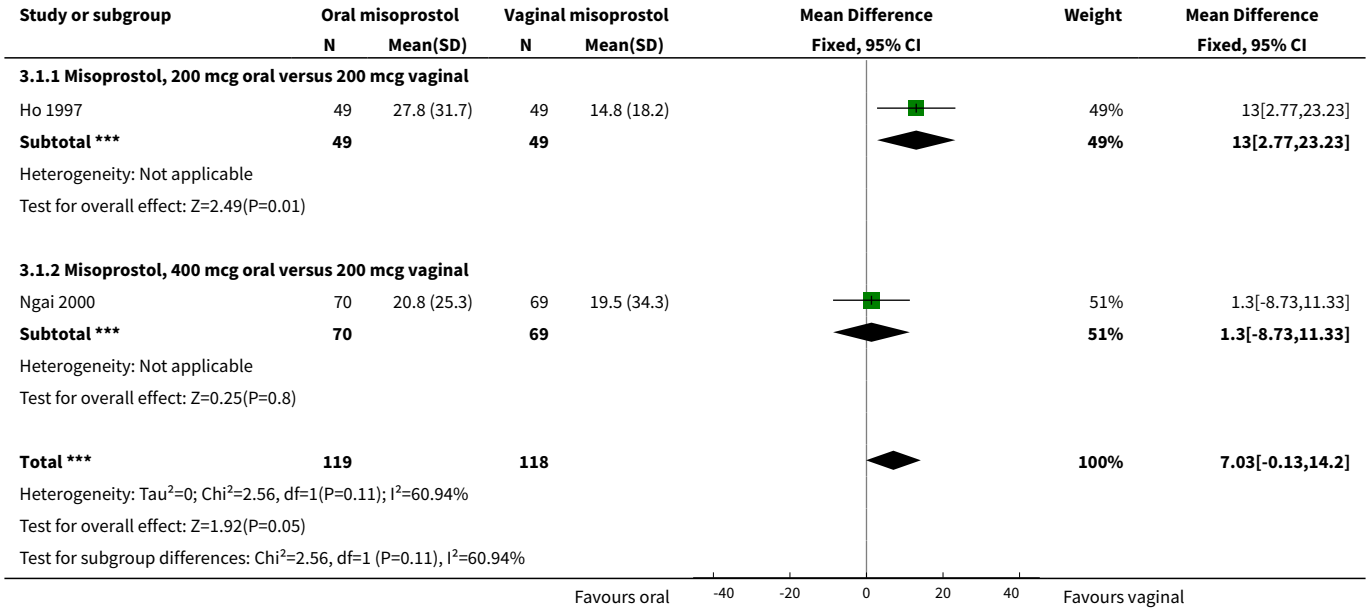
Comparison 3. Comparison: mifepristone+misoprostol, vaginal versus oral

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	2	237	Mean Difference (IV, Fixed, 95% CI)	7.03 [-0.13, 14.20]
1.1 Misoprostol, 200 mcg oral versus 200 mcg vaginal	1	98	Mean Difference (IV, Fixed, 95% CI)	13.0 [2.77, 23.23]
1.2 Misoprostol, 400 mcg oral versus 200 mcg vaginal	1	139	Mean Difference (IV, Fixed, 95% CI)	1.30 [-8.73, 11.33]

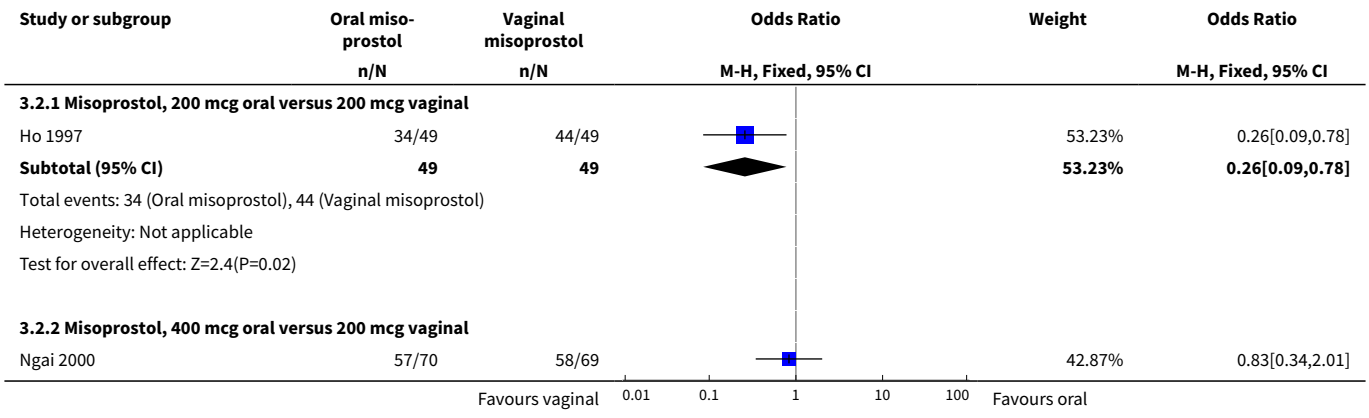
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Abortion within 24 hours	3	306	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.28, 1.02]
2.1 Misoprostol, 200 mcg oral versus 200 mcg vaginal	1	98	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.09, 0.78]
2.2 Misoprostol, 400 mcg oral versus 200 mcg vaginal	1	139	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.34, 2.01]
2.3 Misoprostol, 400 mcg oral versus 400 mcg vaginal	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.06, 16.17]
3 Surgical evacuation	2	208	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.48, 2.04]
3.1 Misoprostol, 400 mcg oral versus 200 mcg vaginal	1	139	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.31, 1.57]
3.2 Misoprostol, 400 mcg oral versus 400 mcg vaginal	1	69	Odds Ratio (M-H, Fixed, 95% CI)	5.86 [0.65, 53.09]
4 Pain	2	208	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.66, 2.62]
4.1 Misoprostol, 400 mcg oral versus 200 mcg vaginal	1	139	Odds Ratio (M-H, Fixed, 95% CI)	1.1 [0.43, 2.79]
4.2 Misoprostol, 400 mcg oral versus 400 mcg vaginal	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.64 [0.59, 4.57]
5 Nausea	2	237	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.61, 1.70]
5.1 Misoprostol, 200 mcg oral versus 200 mcg vaginal	1	98	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.28, 1.47]
5.2 Misoprostol, 400 mcg oral versus 200 mcg vaginal	1	139	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [0.70, 2.68]
6 Vomiting	3	306	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.61, 1.56]
6.1 Misoprostol, 200 mcg oral versus 200 mcg vaginal	1	98	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.25, 1.63]
6.2 Misoprostol, 400 mcg oral versus 200 mcg vaginal	1	139	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.56, 2.15]
6.3 Misoprostol, 400 mcg oral versus 400 mcg vaginal	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.46, 3.17]
7 Diarrhoea	3	306	Odds Ratio (M-H, Fixed, 95% CI)	1.95 [1.18, 3.22]

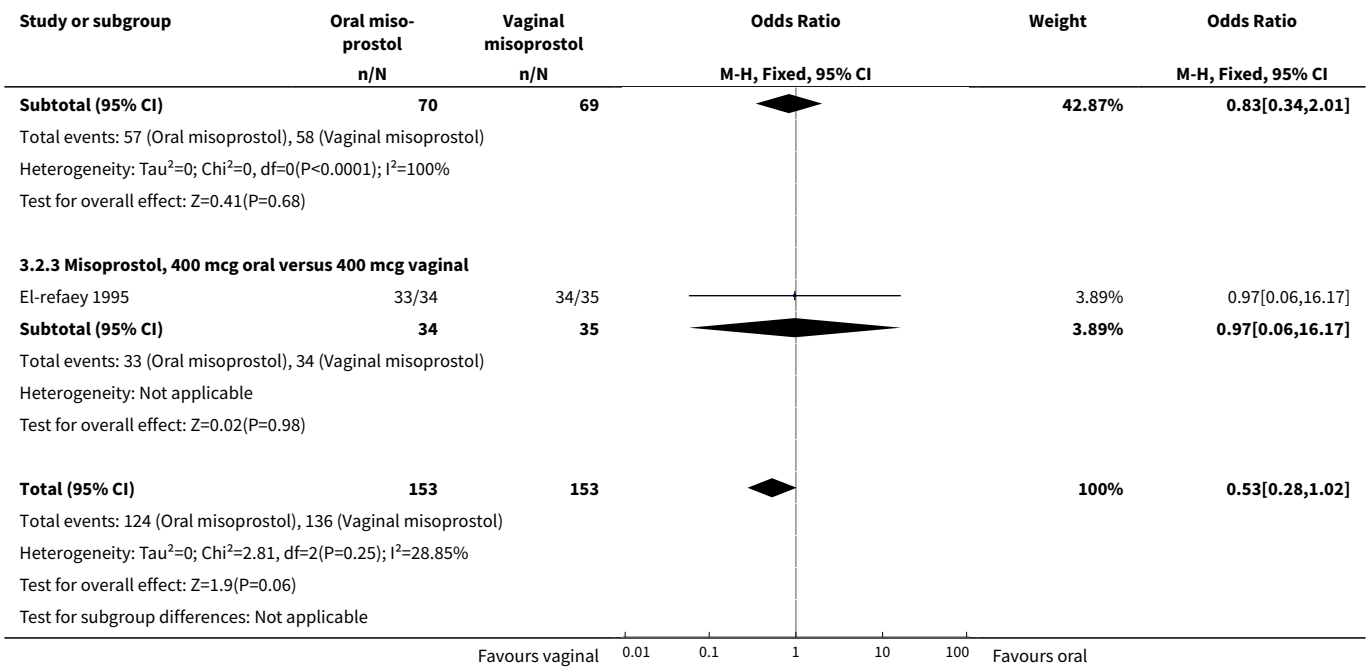
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Misoprostol, 200 mcg oral versus 200 mcg vaginal	1	98	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [0.84, 5.50]
7.2 Misoprostol, 400 mcg oral versus 200 mcg vaginal	1	139	Odds Ratio (M-H, Fixed, 95% CI)	2.21 [1.06, 4.61]
7.3 Misoprostol, 400 mcg oral versus 400 mcg vaginal	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.49, 3.77]

Analysis 3.1. Comparison 3 Comparison: mifepristone+misoprostol, vaginal versus oral, Outcome 1 Induction to abortion interval.

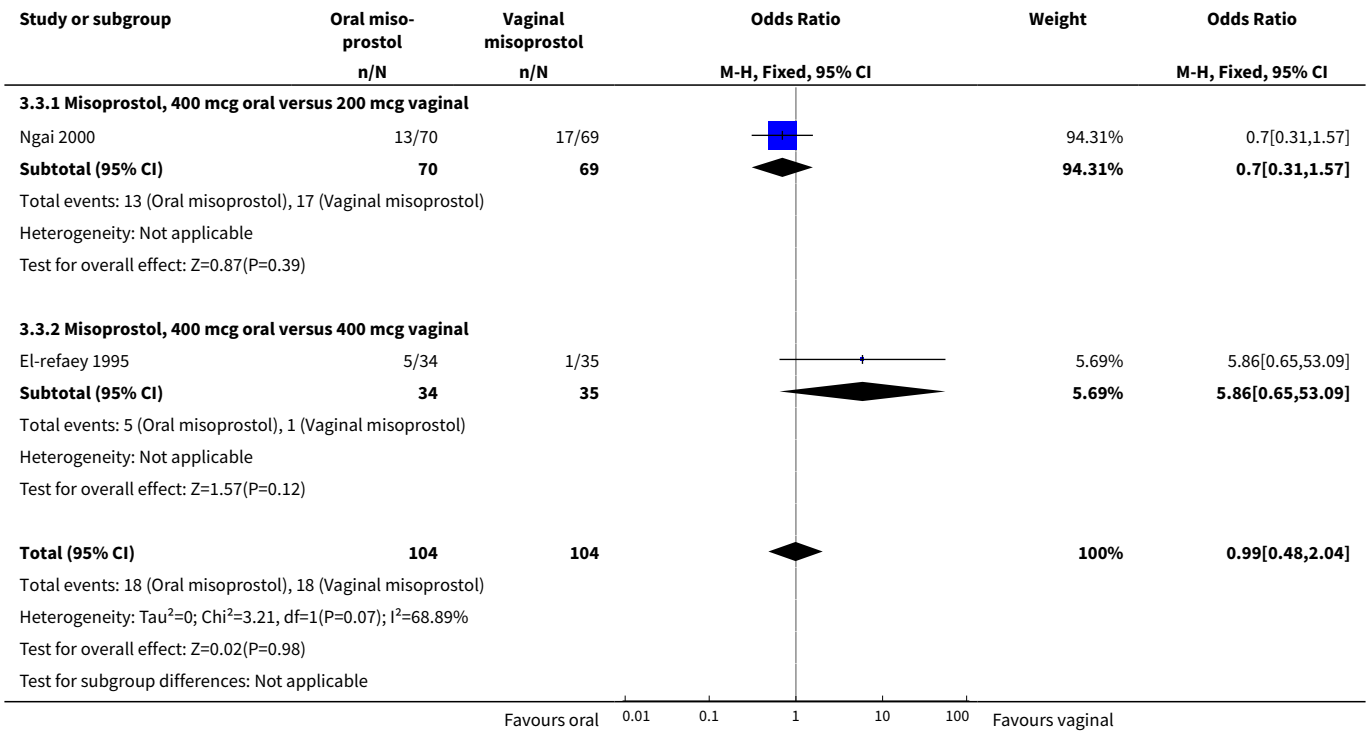


Analysis 3.2. Comparison 3 Comparison: mifepristone+misoprostol, vaginal versus oral, Outcome 2 Abortion within 24 hours.





Analysis 3.3. Comparison 3 Comparison: mifepristone +misoprostol, vaginal versus oral, Outcome 3 Surgical evacuation.



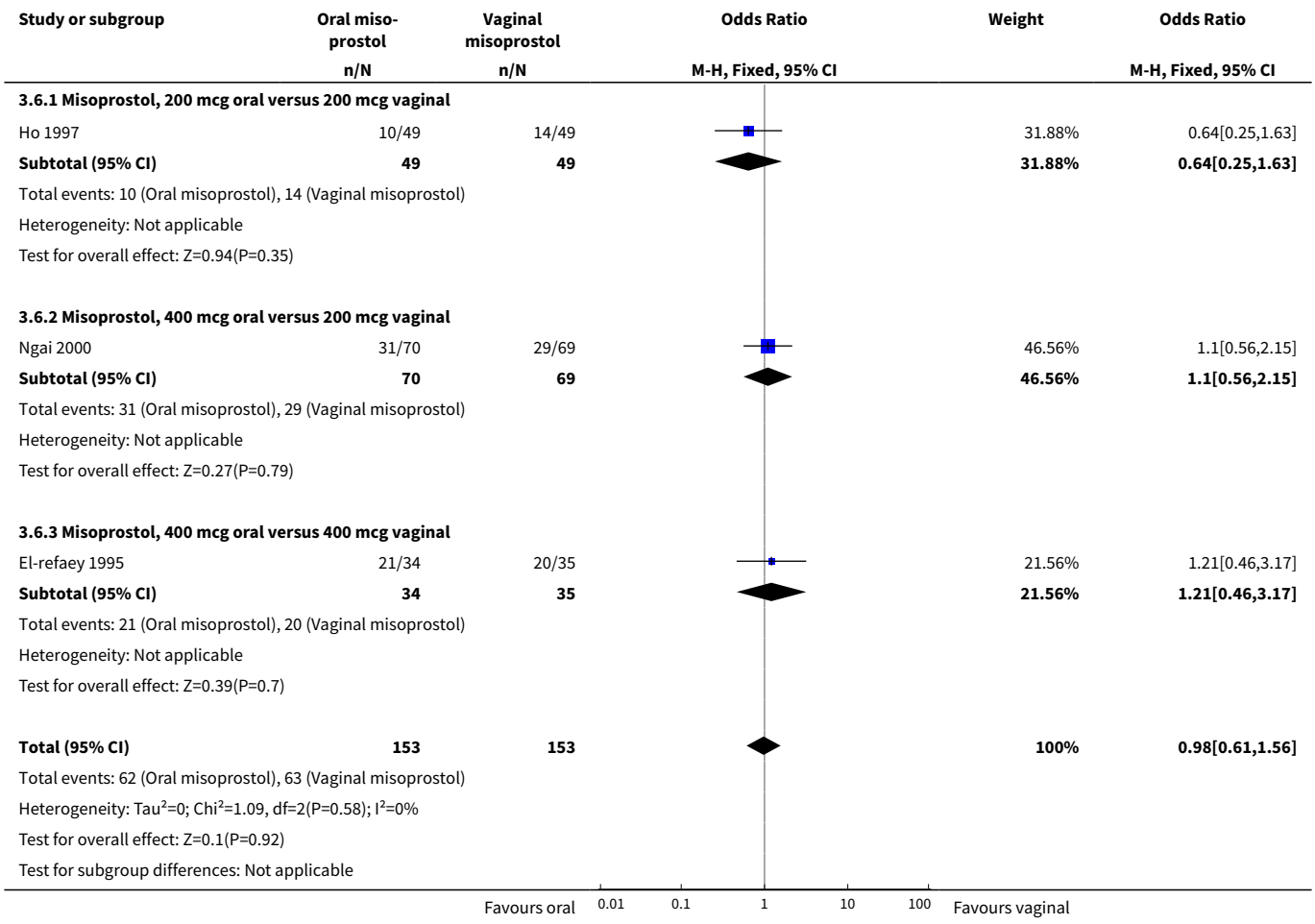
Analysis 3.4. Comparison 3 Comparison: mifepristone+misoprostol, vaginal versus oral, Outcome 4 Pain.

Study or subgroup	Oral misoprostol n/N	Vaginal misoprostol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.4.1 Misoprostol, 400 mcg oral versus 200 mcg vaginal					
Ngai 2000	11/70	10/69		59.66%	1.1[0.43,2.79]
Subtotal (95% CI)	**70**	**69**		**59.66%**	**1.1[0.43,2.79]**
Total events: 11 (Oral misoprostol), 10 (Vaginal misoprostol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.2(P=0.84)					
3.4.2 Misoprostol, 400 mcg oral versus 400 mcg vaginal					
El-refaey 1995	25/34	22/35		40.34%	1.64[0.59,4.57]
Subtotal (95% CI)	**34**	**35**		**40.34%**	**1.64[0.59,4.57]**
Total events: 25 (Oral misoprostol), 22 (Vaginal misoprostol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.95(P=0.34)					
Total (95% CI)	**104**	**104**		**100%**	**1.32[0.66,2.62]**
Total events: 36 (Oral misoprostol), 32 (Vaginal misoprostol)					
Heterogeneity: Tau^2=0; Chi^2=0.32, df=1(P=0.57); I^2=0%					
Test for overall effect: Z=0.79(P=0.43)					
Test for subgroup differences: Not applicable					

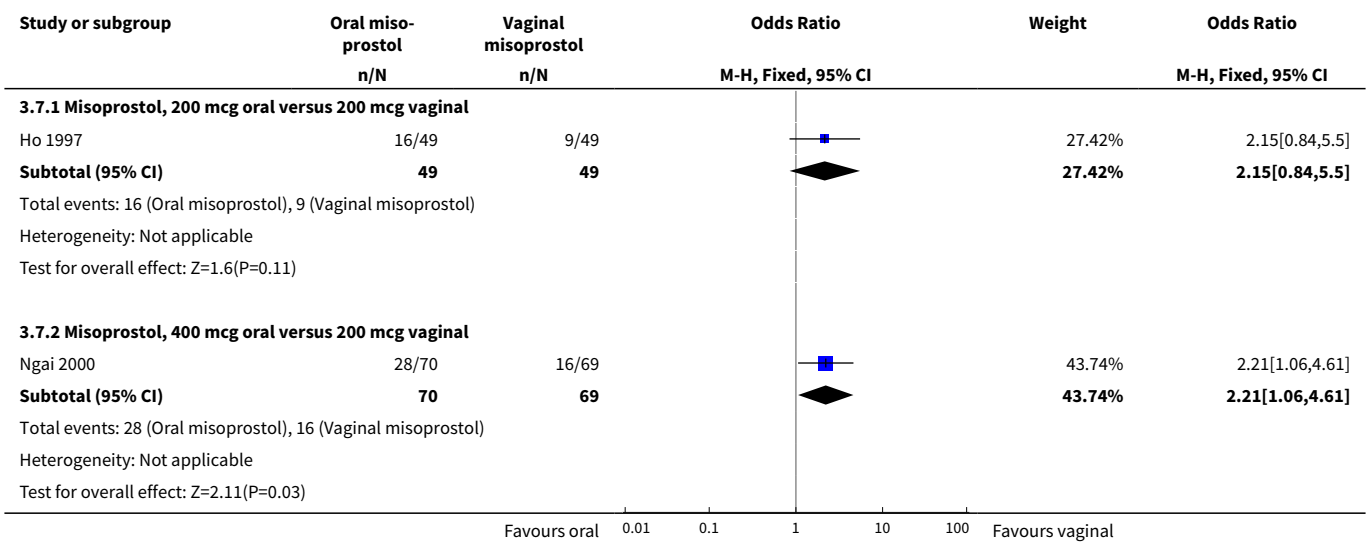
Analysis 3.5. Comparison 3 Comparison: mifepristone+misoprostol, vaginal versus oral, Outcome 5 Nausea.

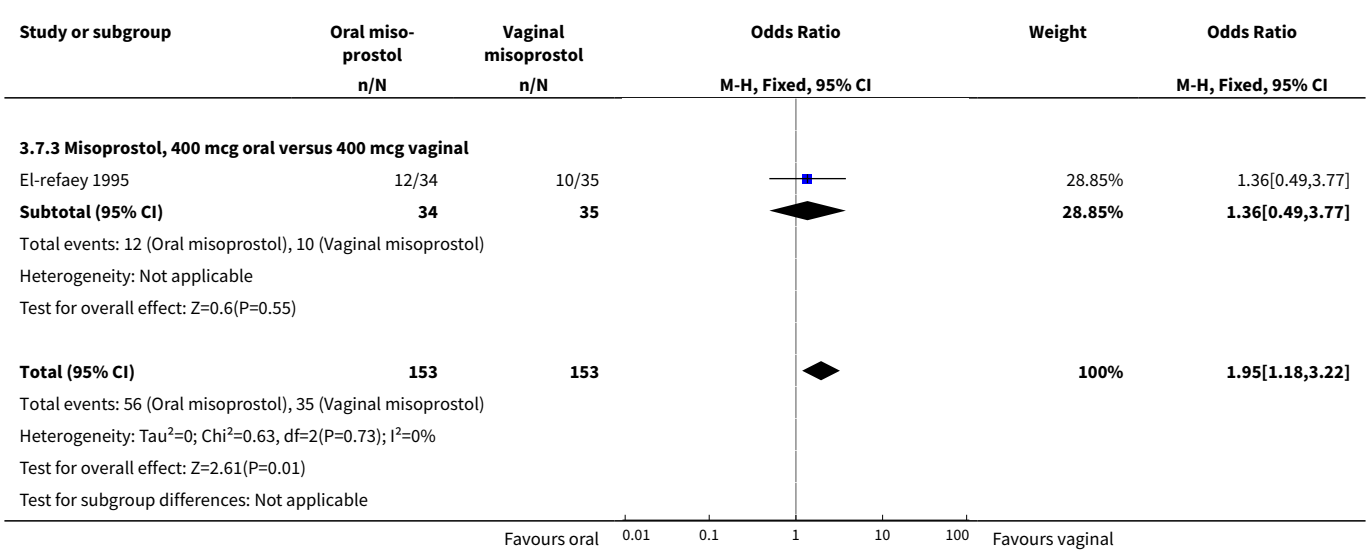
Study or subgroup	Oral misoprostol n/N	Vaginal misoprostol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.5.1 Misoprostol, 200 mcg oral versus 200 mcg vaginal					
Ho 1997	15/49	20/49		48.53%	0.64[0.28,1.47]
Subtotal (95% CI)	**49**	**49**		**48.53%**	**0.64[0.28,1.47]**
Total events: 15 (Oral misoprostol), 20 (Vaginal misoprostol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					
3.5.2 Misoprostol, 400 mcg oral versus 200 mcg vaginal					
Ngai 2000	39/70	33/69		51.47%	1.37[0.7,2.68]
Subtotal (95% CI)	**70**	**69**		**51.47%**	**1.37[0.7,2.68]**
Total events: 39 (Oral misoprostol), 33 (Vaginal misoprostol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.93(P=0.35)					
Total (95% CI)	**119**	**118**		**100%**	**1.02[0.61,1.7]**
Total events: 54 (Oral misoprostol), 53 (Vaginal misoprostol)					
Heterogeneity: Tau^2=0; Chi^2=1.96, df=1(P=0.16); I^2=49.11%					
Test for overall effect: Z=0.06(P=0.95)					
Test for subgroup differences: Not applicable					

Analysis 3.6. Comparison 3 Comparison: mifepristone+misoprostol, vaginal versus oral, Outcome 6 Vomiting.



Analysis 3.7. Comparison 3 Comparison: mifepristone+misoprostol, vaginal versus oral, Outcome 7 Diarrhoea.

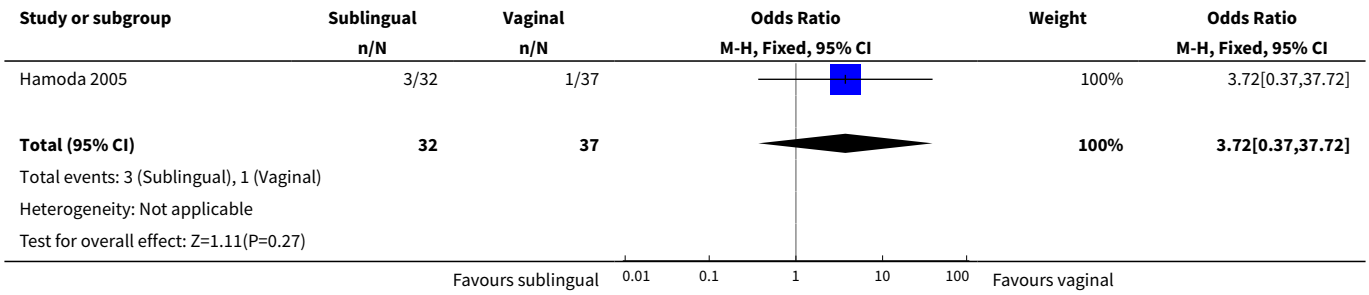




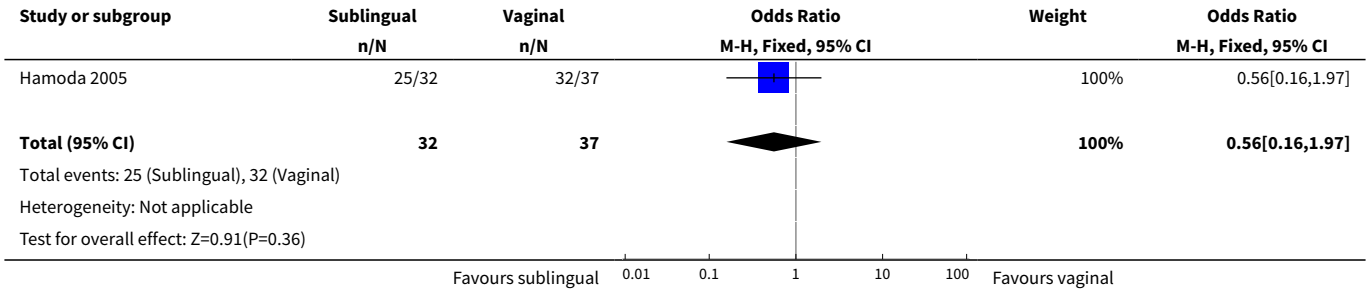
Comparison 4. Comparison: mifepristone+misoprostol, vaginal versus sublingual

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Surgical evacuation	1	69	Odds Ratio (M-H, Fixed, 95% CI)	3.72 [0.37, 37.72]
2 Pain	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.16, 1.97]
3 Nausea	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.83 [0.59, 5.70]
4 Vomiting	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.58, 5.07]
5 Diarrhoea	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.43, 2.91]

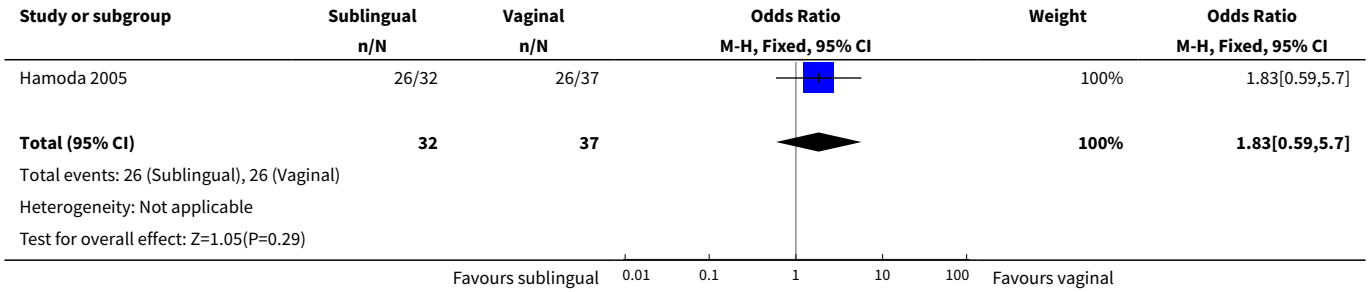
Analysis 4.1. Comparison 4 Comparison: mifepristone+misoprostol, vaginal versus sublingual, Outcome 1 Surgical evacuation.



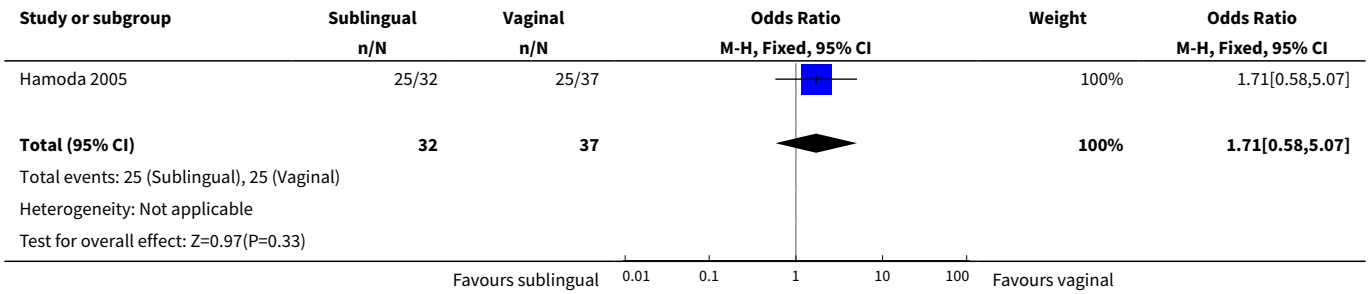
Analysis 4.2. Comparison 4 Comparison: mifepristone+misoprostol, vaginal versus sublingual, Outcome 2 Pain.



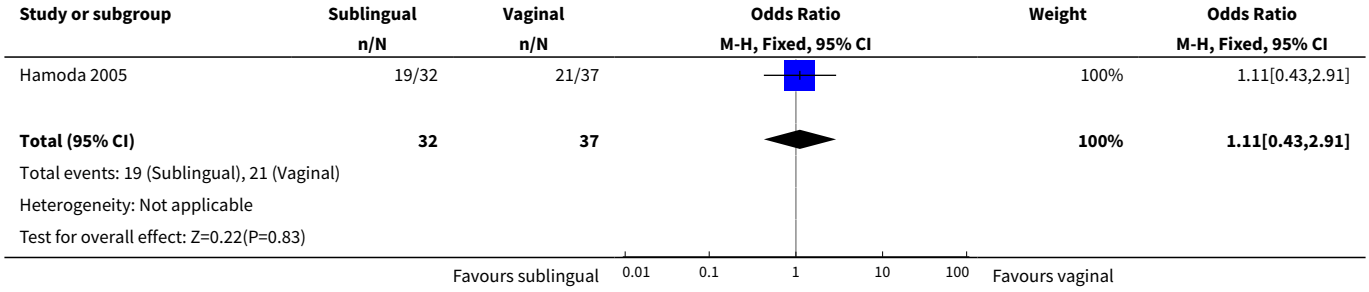
Analysis 4.3. Comparison 4 Comparison: mifepristone+misoprostol, vaginal versus sublingual, Outcome 3 Nausea.



Analysis 4.4. Comparison 4 Comparison: mifepristone+misoprostol, vaginal versus sublingual, Outcome 4 Vomiting.



Analysis 4.5. Comparison 4 Comparison: mifepristone +misoprostol, vaginal versus sublingual, Outcome 5 Diarrhoea.



Comparison 5. Comparison: mifepristone+misoprostol, oral versus sublingual

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abortion within 24h	1	118	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.17, 1.70]
2 Pain (need of analgesic)	1	118	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.40, 1.94]
3 Nausea	1	118	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.60, 2.61]
4 Diarrhoea	1	118	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [0.66, 4.54]

Analysis 5.1. Comparison 5 Comparison: mifepristone +misoprostol, oral versus sublingual, Outcome 1 Abortion within 24h.

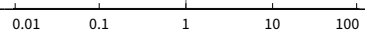
Study or subgroup	Oral n/N	Sublingual n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Tang 2005	51/60	53/58		100%	0.53[0.17,1.7]
Total (95% CI)	**60**	**58**		**100%**	**0.53[0.17,1.7]**
Total events: 51 (Oral), 53 (Sublingual)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.06(P=0.29)					

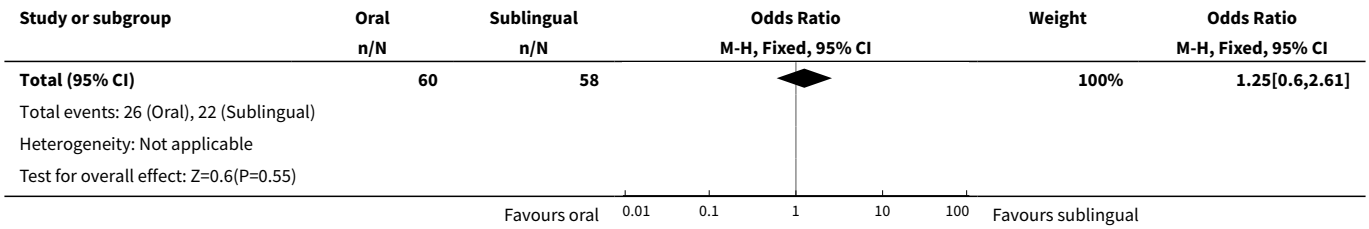
Analysis 5.2. Comparison 5 Comparison: mifepristone+misoprostol, oral versus sublingual, Outcome 2 Pain (need of analgesic).

Study or subgroup	Oral n/N	Sublingual n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Tang 2005	17/60	18/58		100%	0.88[0.4,1.94]
Total (95% CI)	**60**	**58**		**100%**	**0.88[0.4,1.94]**
Total events: 17 (Oral), 18 (Sublingual)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.32(P=0.75)					

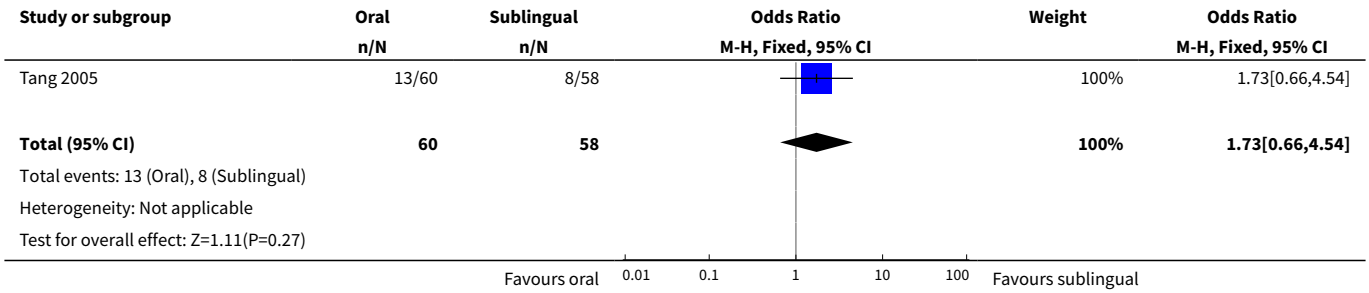
Analysis 5.3. Comparison 5 Comparison: mifepristone+misoprostol, oral versus sublingual, Outcome 3 Nausea.

Study or subgroup	Oral n/N	Sublingual n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Tang 2005	26/60	22/58		100%	1.25[0.6,2.61]





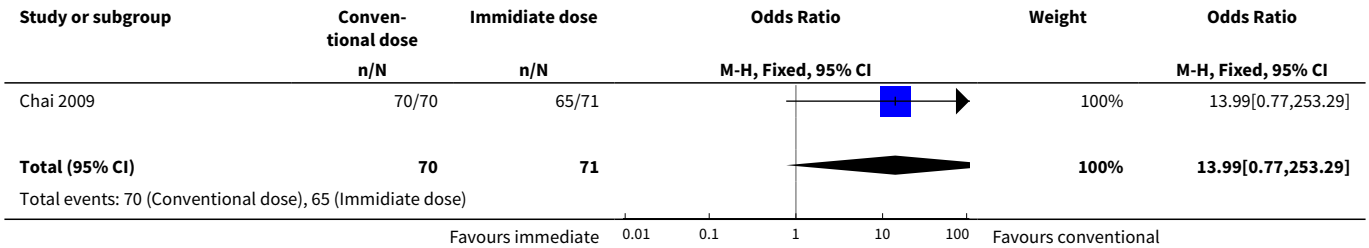
Analysis 5.4. Comparison 5 Comparison: mifepristone+misoprostol, oral versus sublingual, Outcome 4 Diarrhoea.

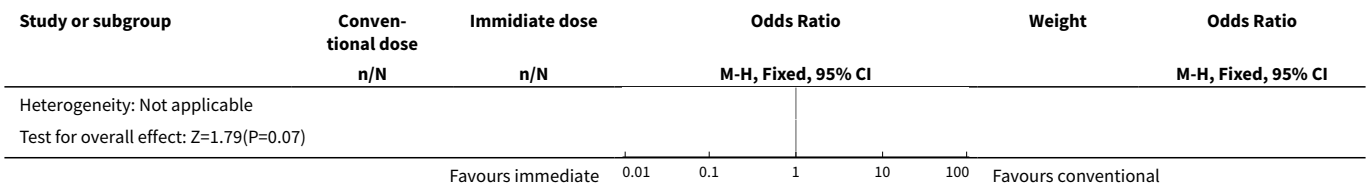


Comparison 6. Comparison: dosing interval of misoprostol following mifepristone

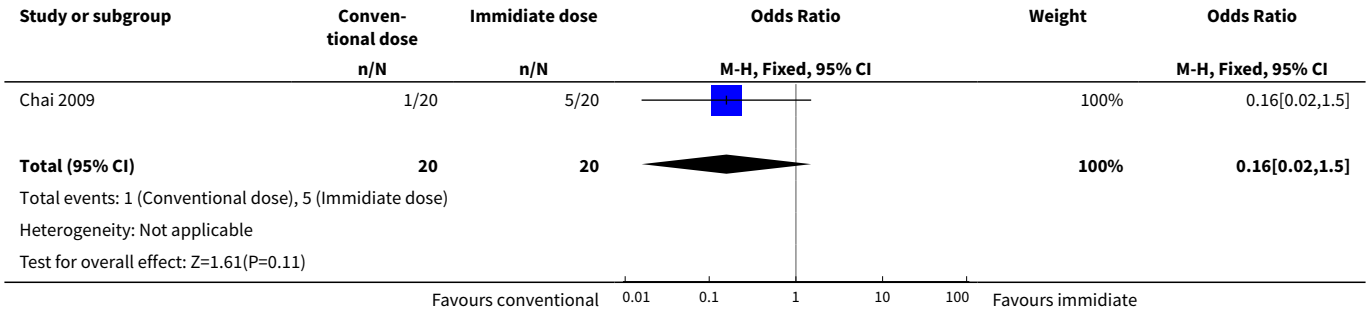
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abortion within 24 hours	1	141	Odds Ratio (M-H, Fixed, 95% CI)	13.99 [0.77, 253.29]
2 Surgical evacuation	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.50]
3 Pain (need for analgesia)	1	141	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.20, 1.67]
4 Nausea	1	141	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.50, 1.89]
5 Diarrhoea	1	141	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.21, 1.16]

Analysis 6.1. Comparison 6 Comparison: dosing interval of misoprostol following mifepristone, Outcome 1 Abortion within 24 hours.

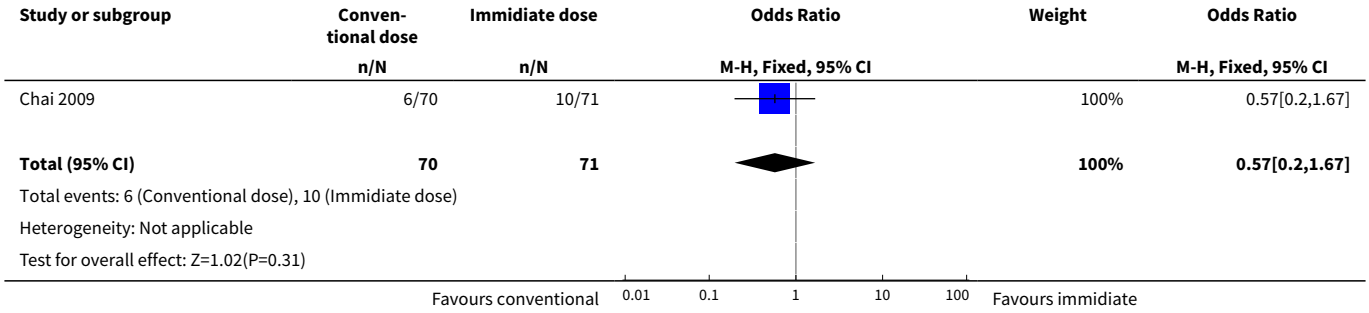




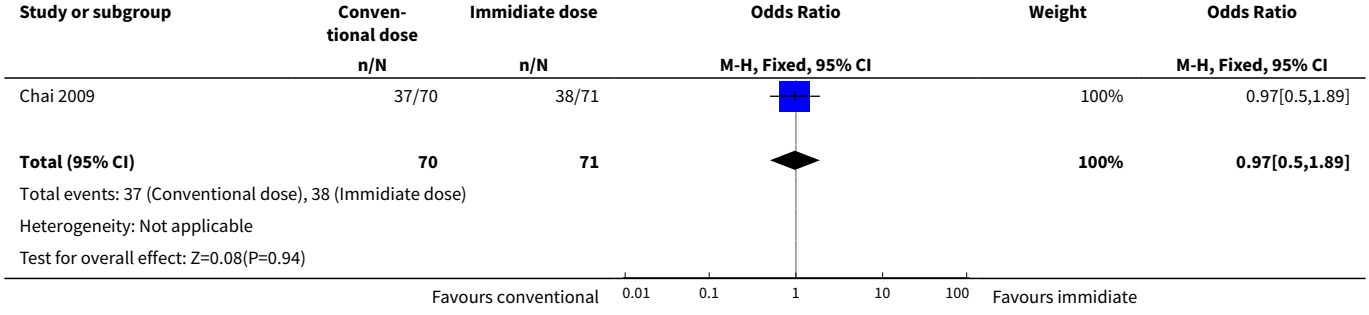
Analysis 6.2. Comparison 6 Comparison: dosing interval of misoprostol following mifepristone, Outcome 2 Surgical evacuation.



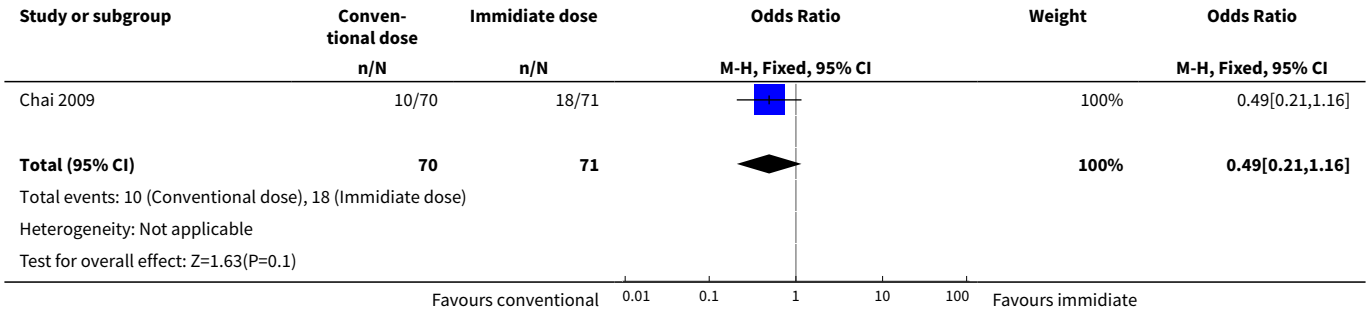
Analysis 6.3. Comparison 6 Comparison: dosing interval of misoprostol following mifepristone, Outcome 3 Pain (need for analgesia).



Analysis 6.4. Comparison 6 Comparison: dosing interval of misoprostol following mifepristone, Outcome 4 Nausea.



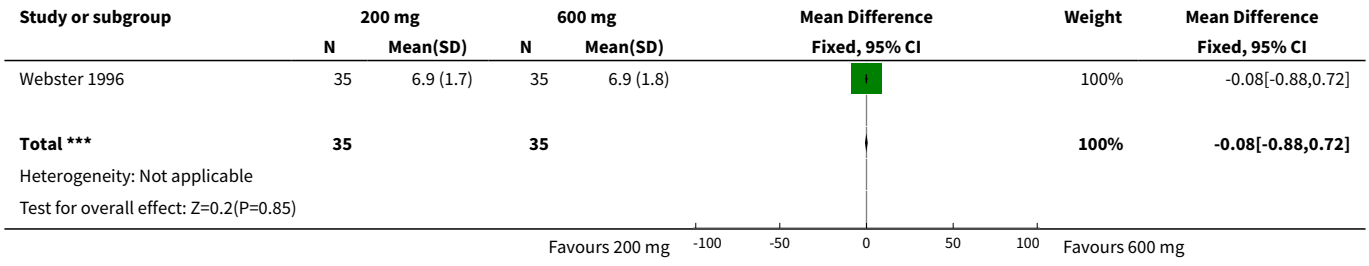
Analysis 6.5. Comparison 6 Comparison: dosing interval of misoprostol following mifepristone, Outcome 5 Diarrhoea.



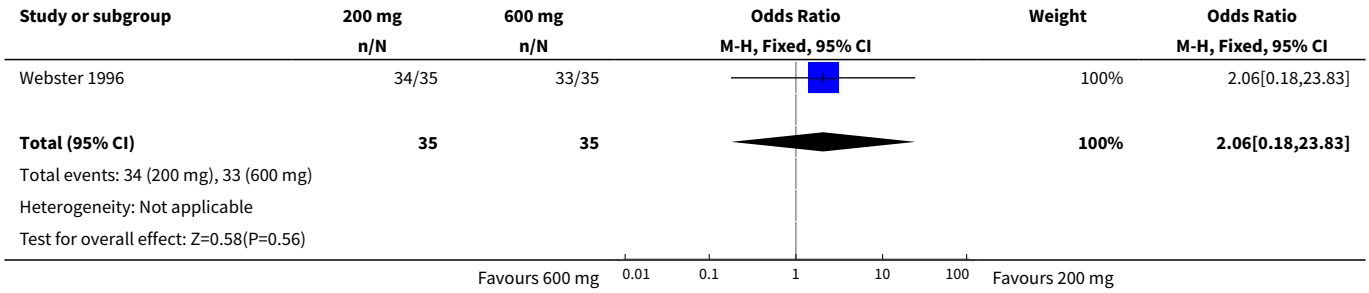
Comparison 7. Comparison: dosage of mifepristone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	1	70	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.88, 0.72]
2 Abortion within 24h	1	70	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.18, 23.83]
3 Surgical evacuation	1	70	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.12, 2.56]
4 Pain	1	70	Odds Ratio (M-H, Fixed, 95% CI)	2.03 [0.78, 5.31]
5 Vomiting	1	70	Odds Ratio (M-H, Fixed, 95% CI)	2.25 [0.86, 5.85]
6 Diarrhoea	1	70	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.34, 2.92]

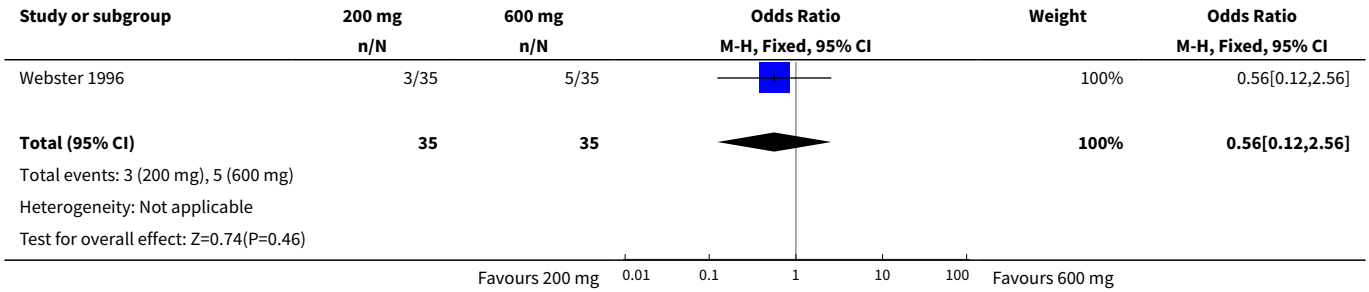
Analysis 7.1. Comparison 7 Comparison: dosage of mifepristone, Outcome 1 Induction to abortion interval.



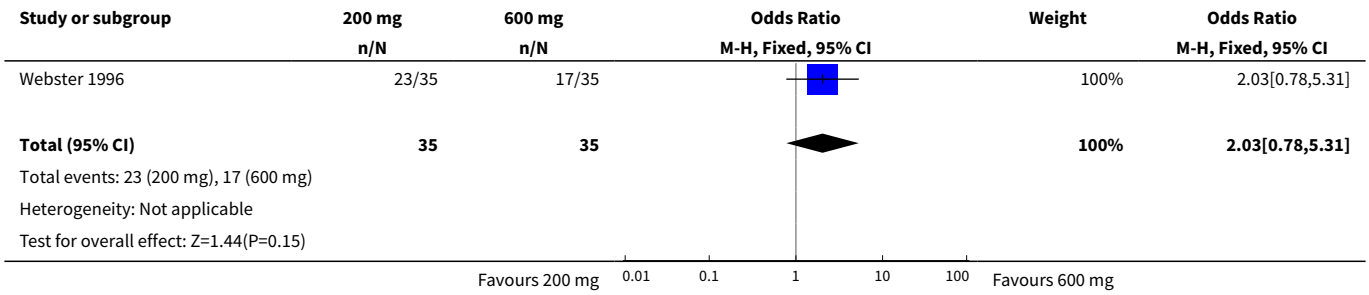
Analysis 7.2. Comparison 7 Comparison: dosage of mifepristone, Outcome 2 Abortion within 24h.



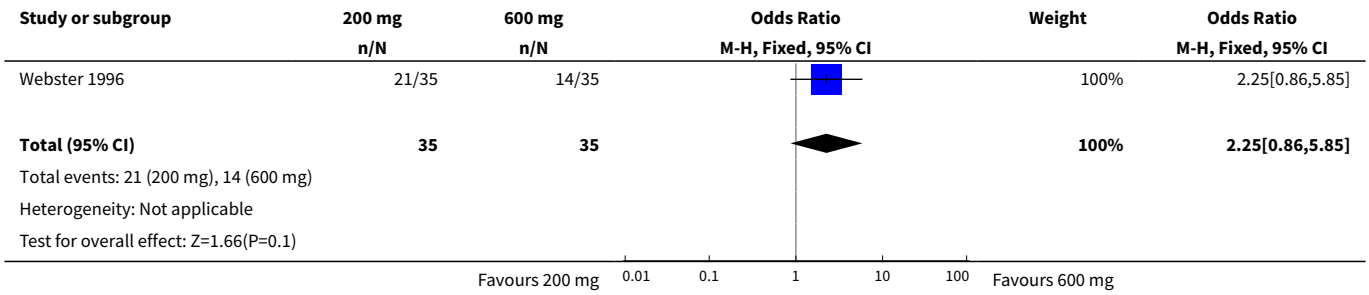
Analysis 7.3. Comparison 7 Comparison: dosage of mifepristone, Outcome 3 Surgical evacuation.



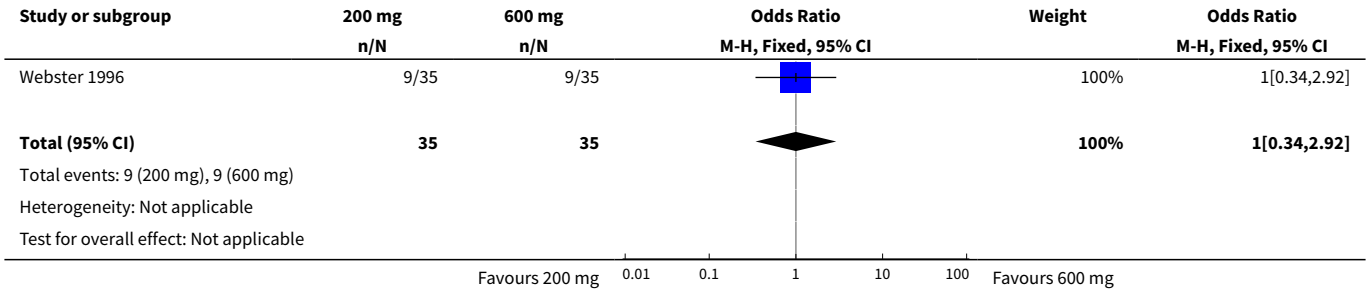
Analysis 7.4. Comparison 7 Comparison: dosage of mifepristone, Outcome 4 Pain.



Analysis 7.5. Comparison 7 Comparison: dosage of mifepristone, Outcome 5 Vomiting.



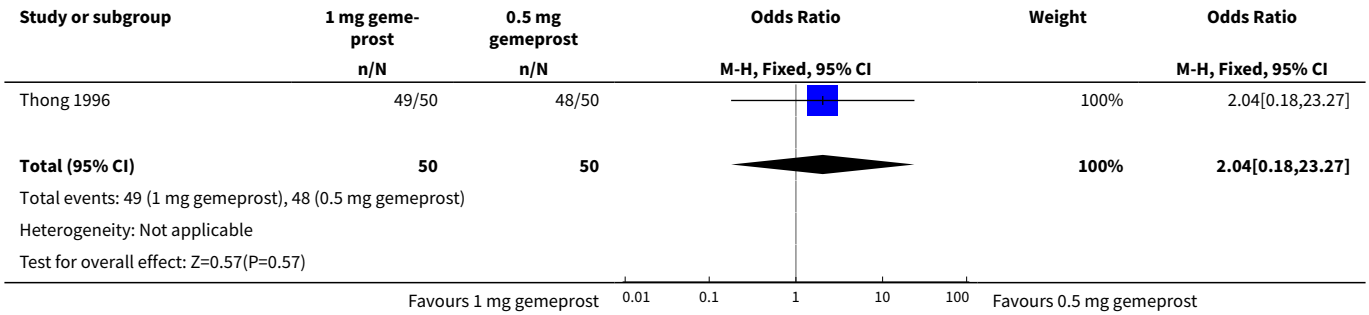
Analysis 7.6. Comparison 7 Comparison: dosage of mifepristone, Outcome 6 Diarrhoea.



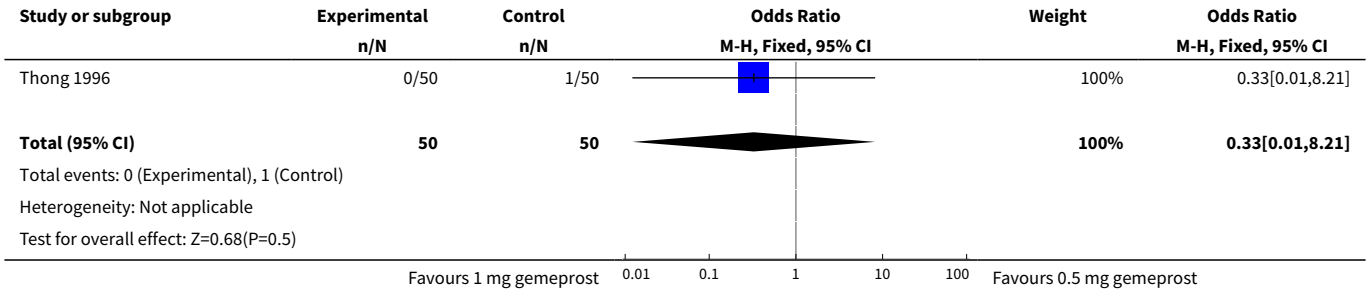
Comparison 8. Comparison: combined regimen of mifepristone and gemeprost

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abortion within 24 hours	1	100	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [0.18, 23.27]
2 Blood loss	1	100	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.21]
3 Surgical evacuation	1	100	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.55, 3.80]
4 Vomiting	1	90	Odds Ratio (M-H, Fixed, 95% CI)	2.83 [1.04, 7.66]
5 Diarrhoea	1	100	Odds Ratio (M-H, Fixed, 95% CI)	3.27 [0.63, 17.07]

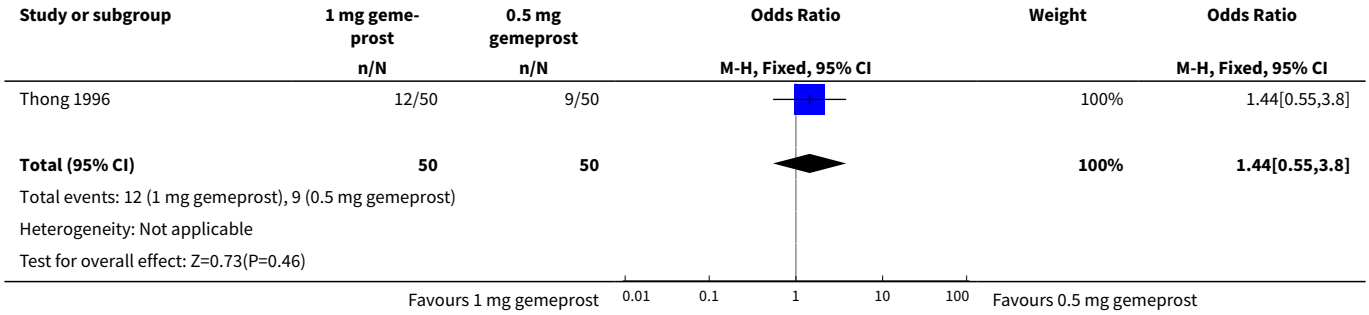
Analysis 8.1. Comparison 8 Comparison: combined regimen of mifepristone and gemeprost, Outcome 1 Abortion within 24 hours.



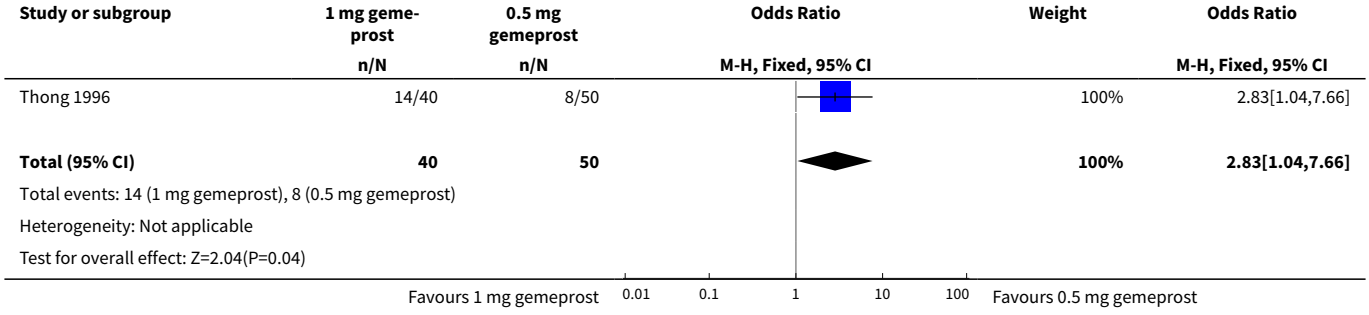
Analysis 8.2. Comparison 8 Comparison: combined regimen of mifepristone and gemeprost, Outcome 2 Blood loss.



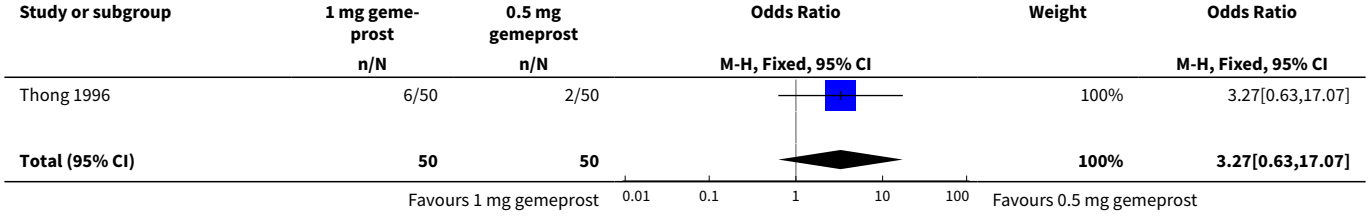
Analysis 8.3. Comparison 8 Comparison: combined regimen of mifepristone and gemeprost, Outcome 3 Surgical evacuation.

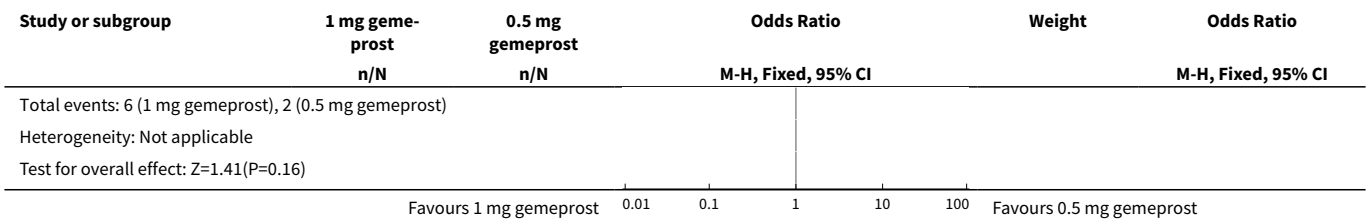


Analysis 8.4. Comparison 8 Comparison: combined regimen of mifepristone and gemeprost, Outcome 4 Vomiting.



Analysis 8.5. Comparison 8 Comparison: combined regimen of mifepristone and gemeprost, Outcome 5 Diarrhoea.

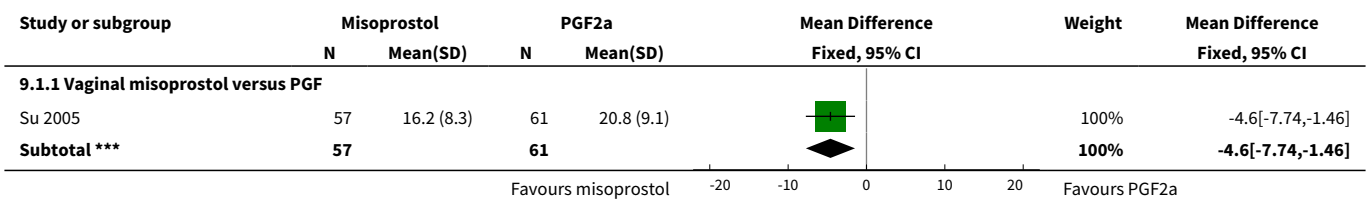


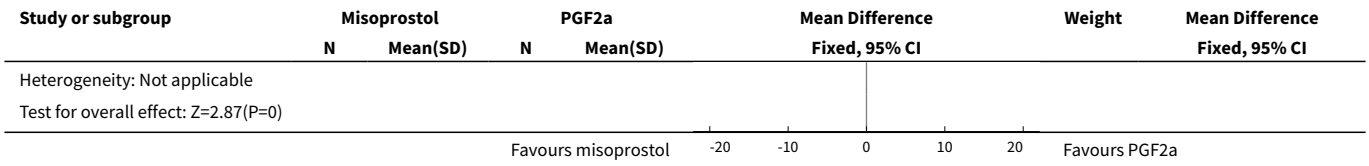


Comparison 9. Comparison: misoprostol versus PGF

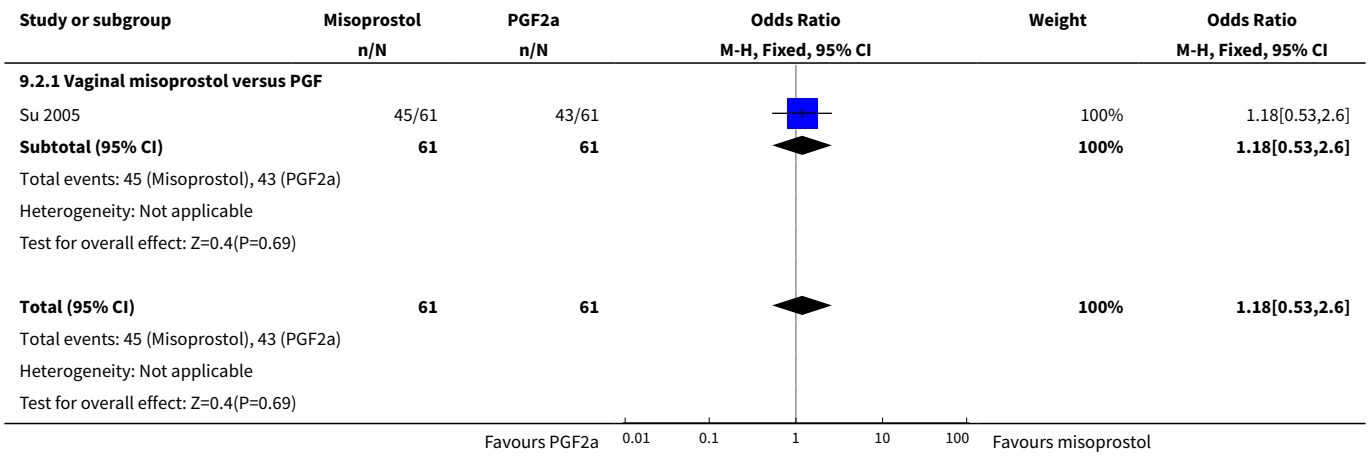
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Vaginal misoprostol versus PGF	1	118	Mean Difference (IV, Fixed, 95% CI)	-4.60 [-7.74, -1.46]
2 Abortion within 24 hours	1	122	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.53, 2.60]
2.1 Vaginal misoprostol versus PGF	1	122	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.53, 2.60]
3 Surgical evacuation	1	122	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.32, 2.02]
3.1 Vaginal misoprostol versus PGF	1	122	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.32, 2.02]
4 Nausea	1	118	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.26, 1.47]
4.1 Vaginal misoprostol versus PGF	1	118	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.26, 1.47]
5 Vomiting	1	118	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.25, 1.59]
5.1 Vaginal misoprostol versus PGF	1	118	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.25, 1.59]
6 Diarrhoea	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Vaginal misoprostol versus PGF	1	118	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.21, 1.14]

Analysis 9.1. Comparison 9 Comparison: misoprostol versus PGF, Outcome 1 Induction to abortion interval.

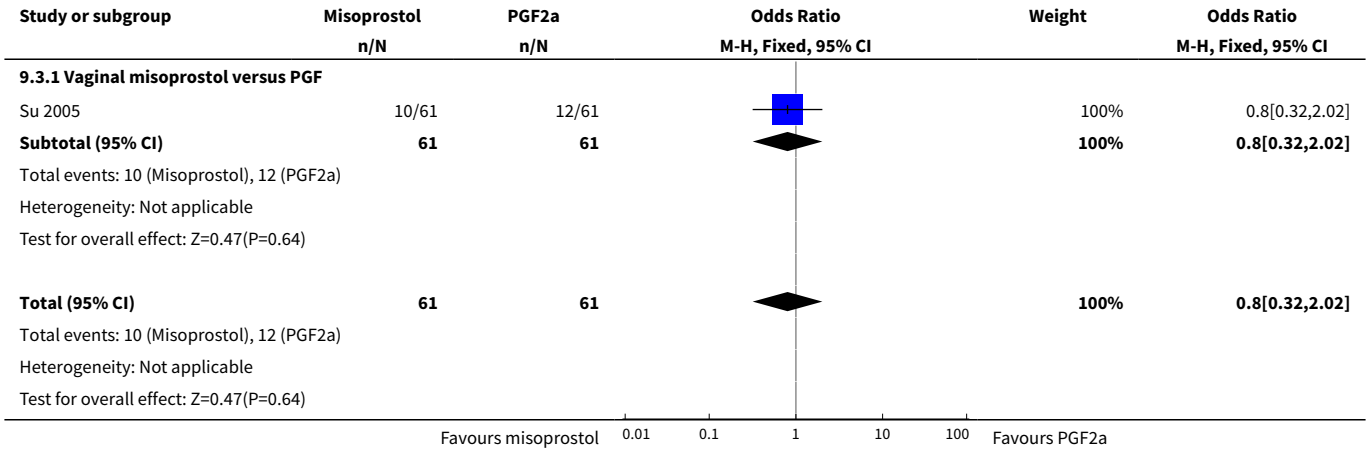




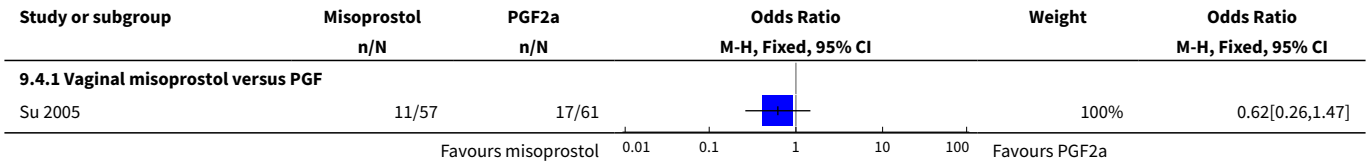
Analysis 9.2. Comparison 9 Comparison: misoprostol versus PGF, Outcome 2 Abortion within 24 hours.

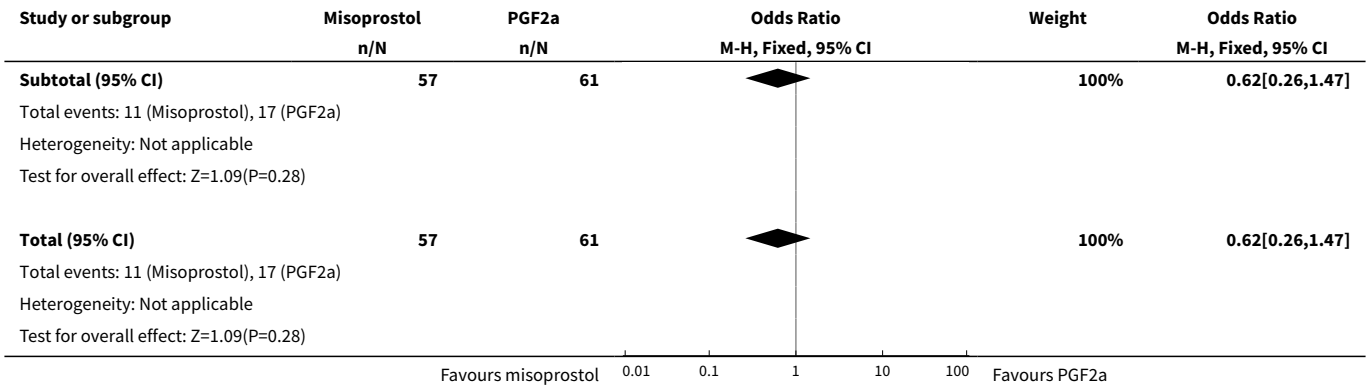


Analysis 9.3. Comparison 9 Comparison: misoprostol versus PGF, Outcome 3 Surgical evacuation.

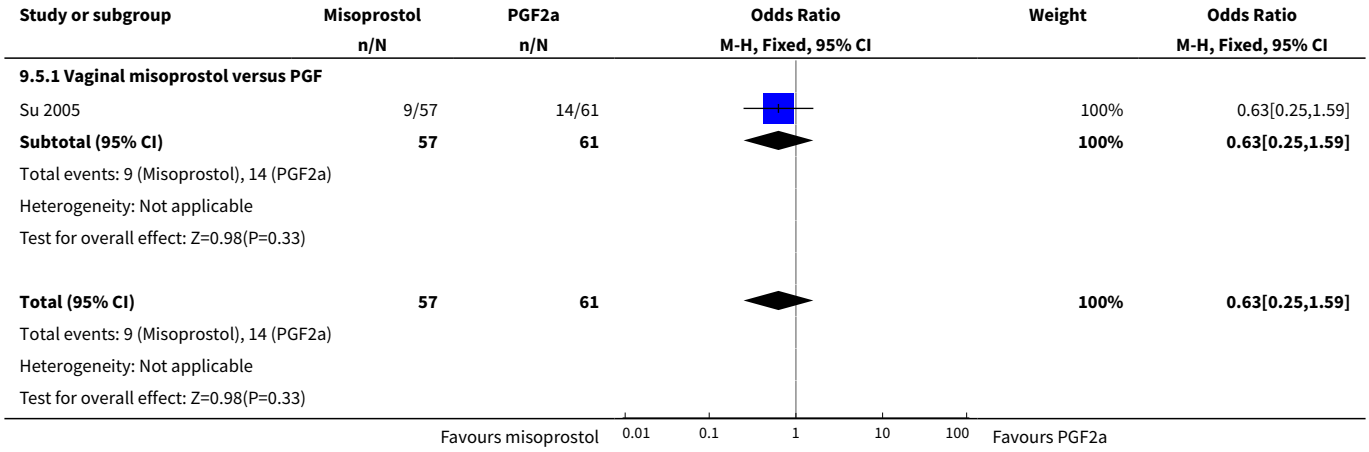


Analysis 9.4. Comparison 9 Comparison: misoprostol versus PGF, Outcome 4 Nausea.

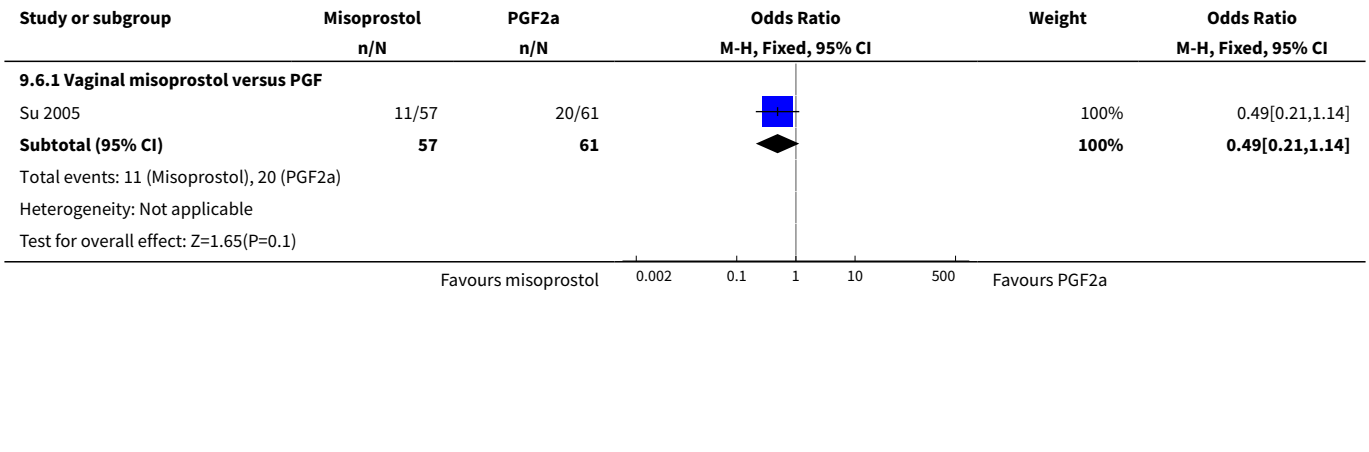




Analysis 9.5. Comparison 9 Comparison: misoprostol versus PGF, Outcome 5 Vomiting.



Analysis 9.6. Comparison 9 Comparison: misoprostol versus PGF, Outcome 6 Diarrhoea.

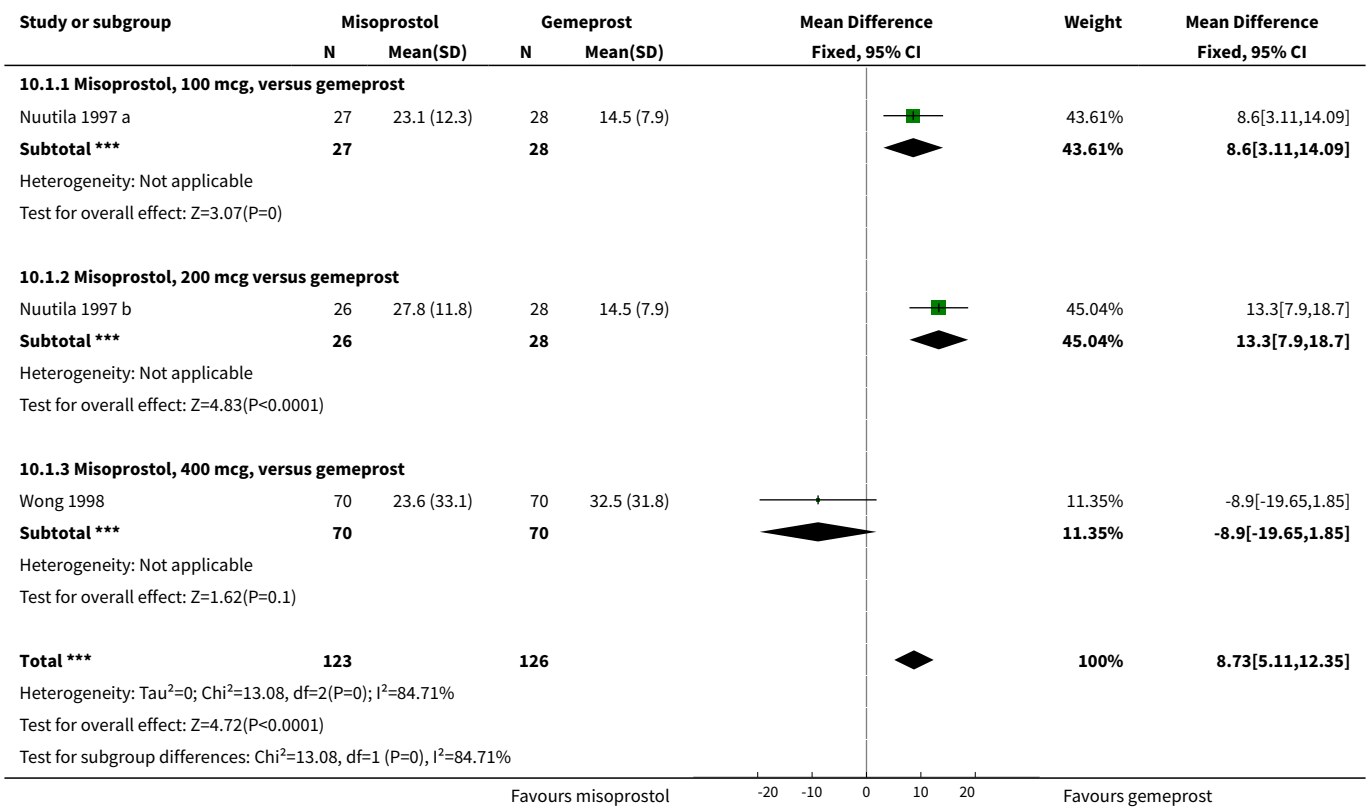


Comparison 10. Comparison: misoprostol versus gemeprost

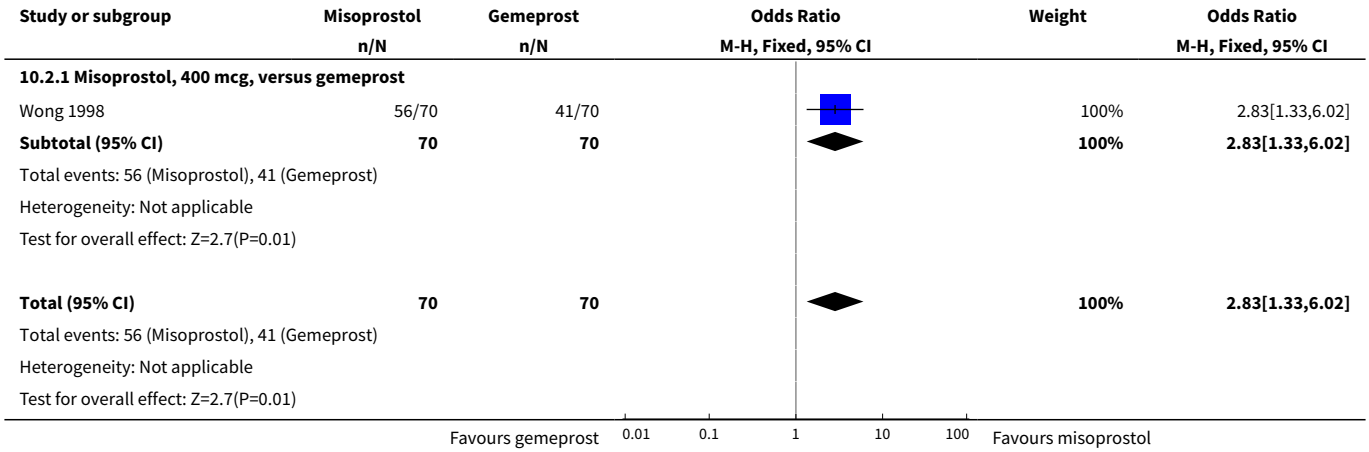
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	3	249	Mean Difference (IV, Fixed, 95% CI)	8.73 [5.11, 12.35]
1.1 Misoprostol, 100 mcg, versus gemeprost	1	55	Mean Difference (IV, Fixed, 95% CI)	8.60 [3.11, 14.09]
1.2 Misoprostol, 200 mcg versus gemeprost	1	54	Mean Difference (IV, Fixed, 95% CI)	13.3 [7.90, 18.70]
1.3 Misoprostol, 400 mcg, versus gemeprost	1	140	Mean Difference (IV, Fixed, 95% CI)	-8.90 [-19.65, 1.85]
2 Abortion within 24 hours	1	140	Odds Ratio (M-H, Fixed, 95% CI)	2.83 [1.33, 6.02]
2.1 Misoprostol, 400 mcg, versus gemeprost	1	140	Odds Ratio (M-H, Fixed, 95% CI)	2.83 [1.33, 6.02]
3 Blood loss (mL)	3	249	Mean Difference (IV, Fixed, 95% CI)	-23.75 [-47.80, 0.30]
3.1 Misoprostol, 100 mcg, versus gemeprost	1	55	Mean Difference (IV, Fixed, 95% CI)	-61.0 [-145.71, 23.71]
3.2 Misoprostol, 200 mcg, versus gemeprost	1	54	Mean Difference (IV, Fixed, 95% CI)	-146.0 [-219.02, -72.98]
3.3 Misoprostol, 400 mcg, versus gemeprost	1	140	Mean Difference (IV, Fixed, 95% CI)	-3.70 [-30.40, 23.00]
4 Surgical evacuation	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.48, 1.85]
4.1 Misoprostol, 400 mcg, versus gemeprost	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.48, 1.85]
5 Pain	2	109	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.10, 0.52]
5.1 Misoprostol, 100 mcg, versus gemeprost	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.07, 0.71]
5.2 Misoprostol, 200 mcg, versus gemeprost	1	54	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.07, 0.77]
6 Nausea	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.38, 1.70]
6.1 Misoprostol, 400 mcg, versus gemeprost	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.38, 1.70]
7 Vomiting	3	249	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.21, 0.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Misoprostol, 100 mcg, versus gemeprost	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.10, 1.06]
7.2 Misoprostol, 200 mcg, versus gemeprost	1	54	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.04, 0.62]
7.3 Misoprostol, 400 mcg, versus gemeprost	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.25, 1.18]
8 Diarrhoea	3	249	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.17, 0.58]
8.1 Misoprostol, 100 mcg, versus gemeprost	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.68]
8.2 Misoprostol, 200 mcg, versus gemeprost	1	54	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.03, 0.91]
8.3 Misoprostol, 400 mcg, versus gemeprost	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.23, 0.99]

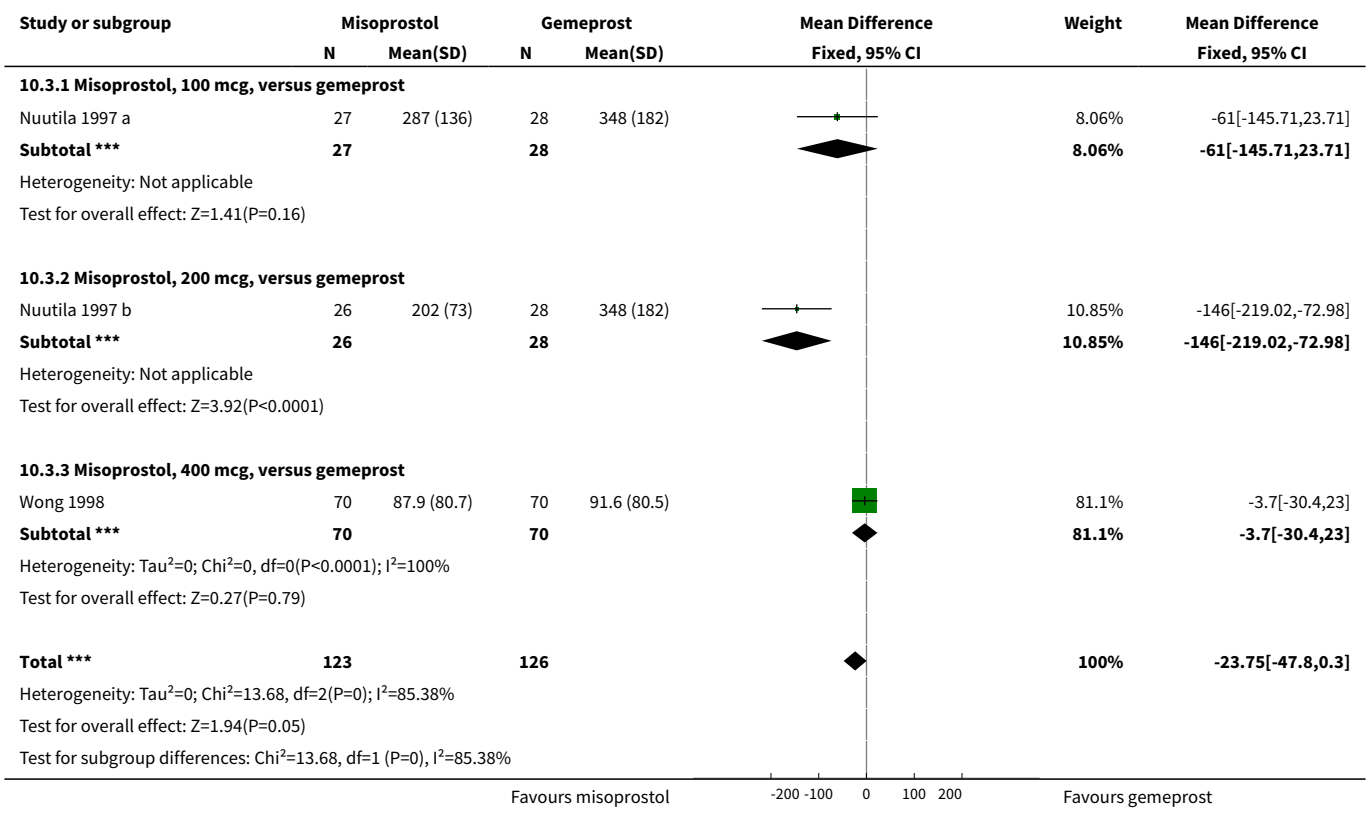
Analysis 10.1. Comparison 10 Comparison: misoprostol versus gemeprost, Outcome 1 Induction to abortion interval.



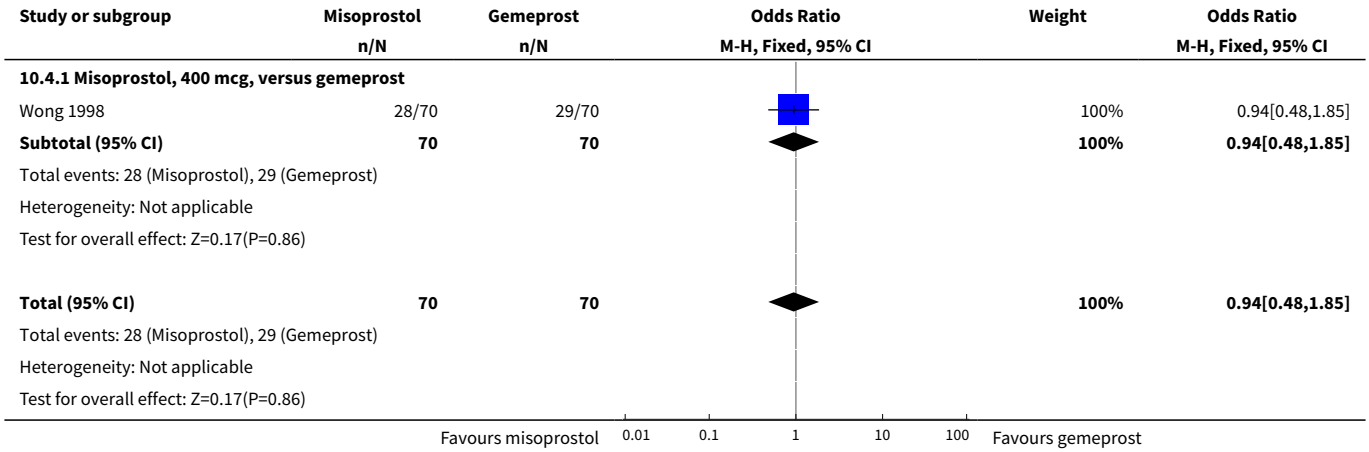
Analysis 10.2. Comparison 10 Comparison: misoprostol versus gemeprost, Outcome 2 Abortion within 24 hours.



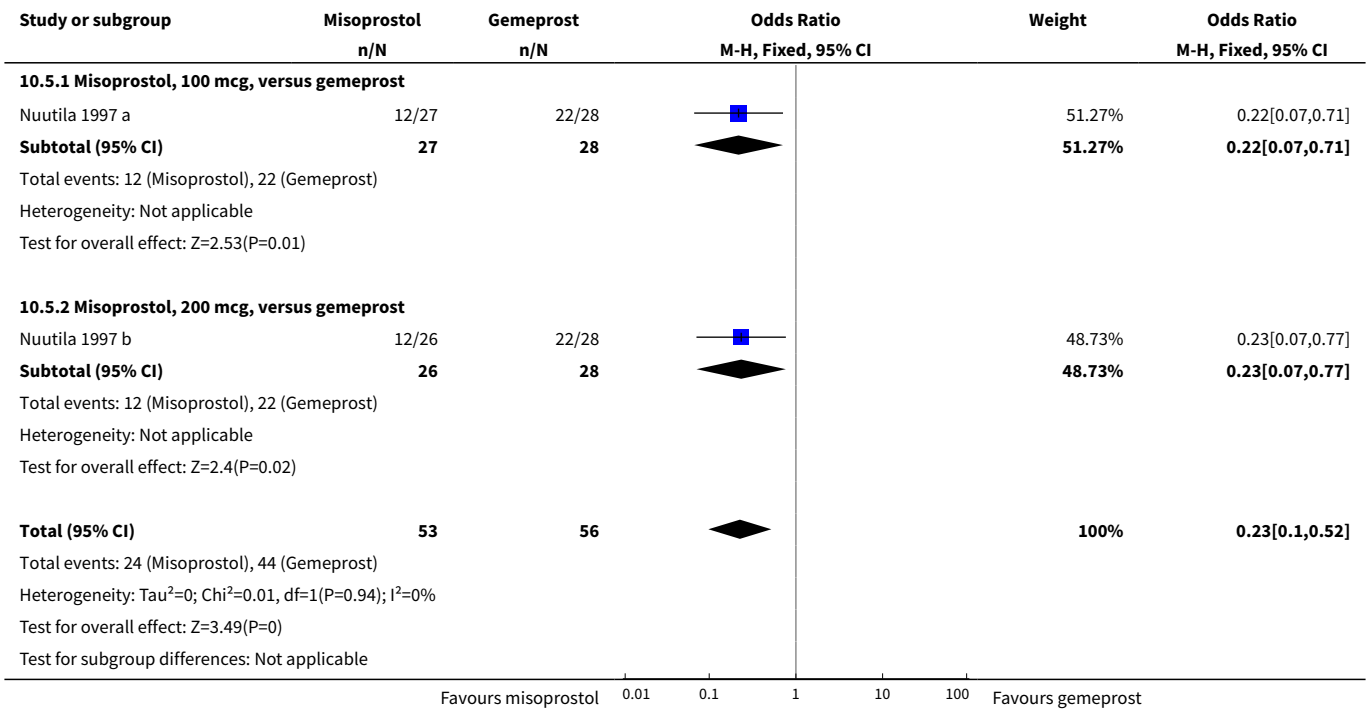
Analysis 10.3. Comparison 10 Comparison: misoprostol versus gemeprost, Outcome 3 Blood loss (mL).



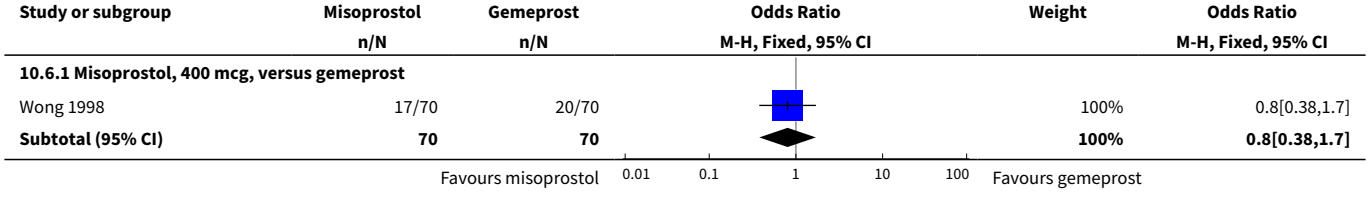
Analysis 10.4. Comparison 10 Comparison: misoprostol versus gemeprost, Outcome 4 Surgical evacuation.

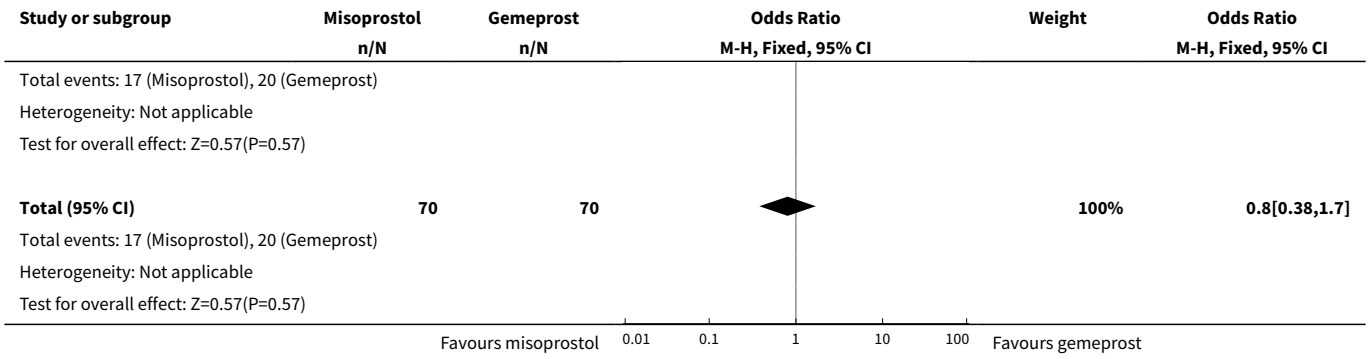


Analysis 10.5. Comparison 10 Comparison: misoprostol versus gemeprost, Outcome 5 Pain.

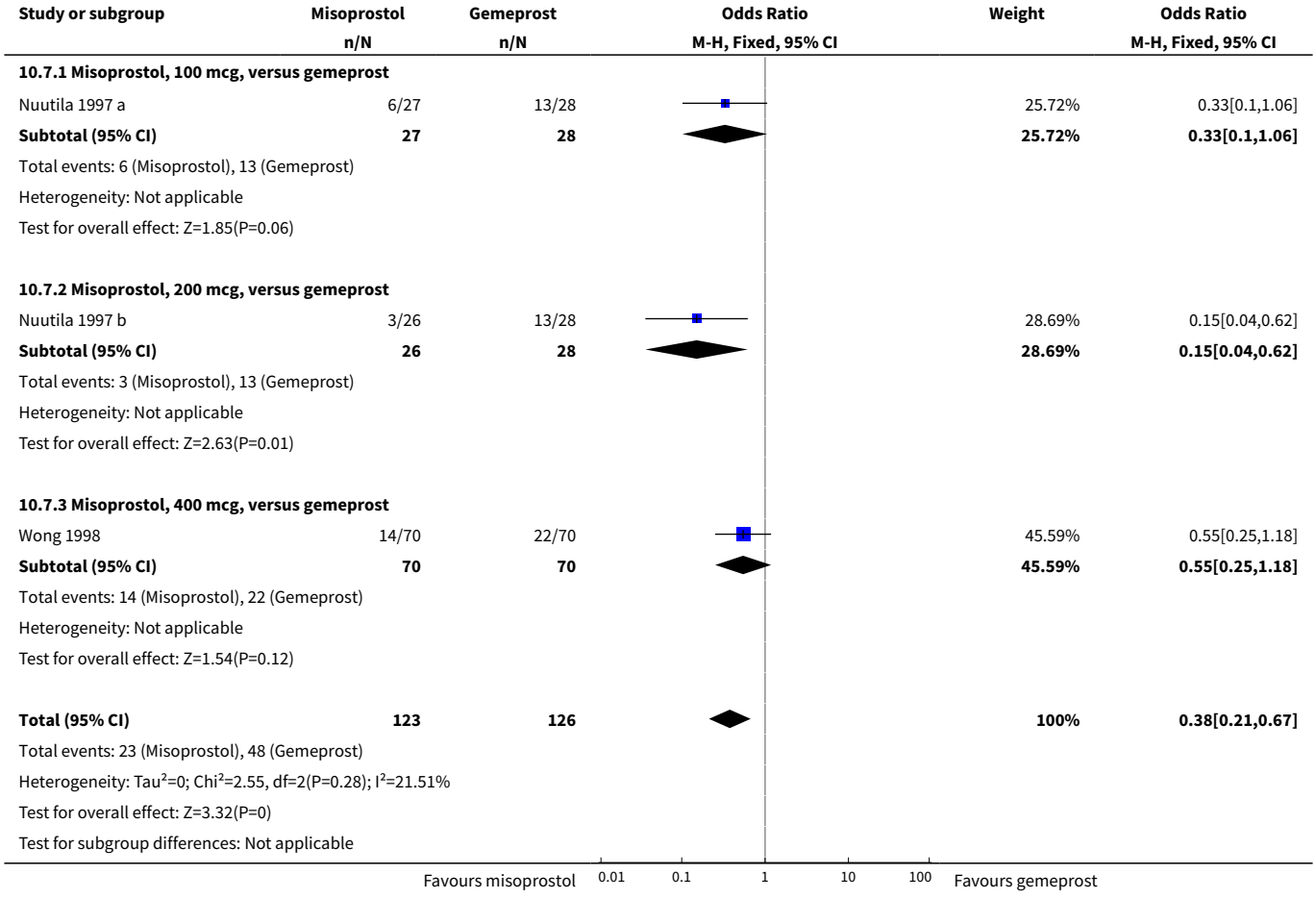


Analysis 10.6. Comparison 10 Comparison: misoprostol versus gemeprost, Outcome 6 Nausea.

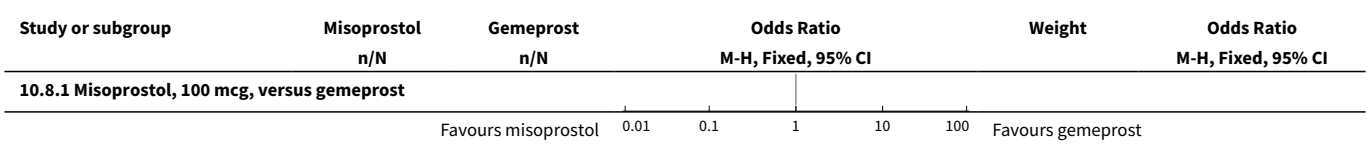


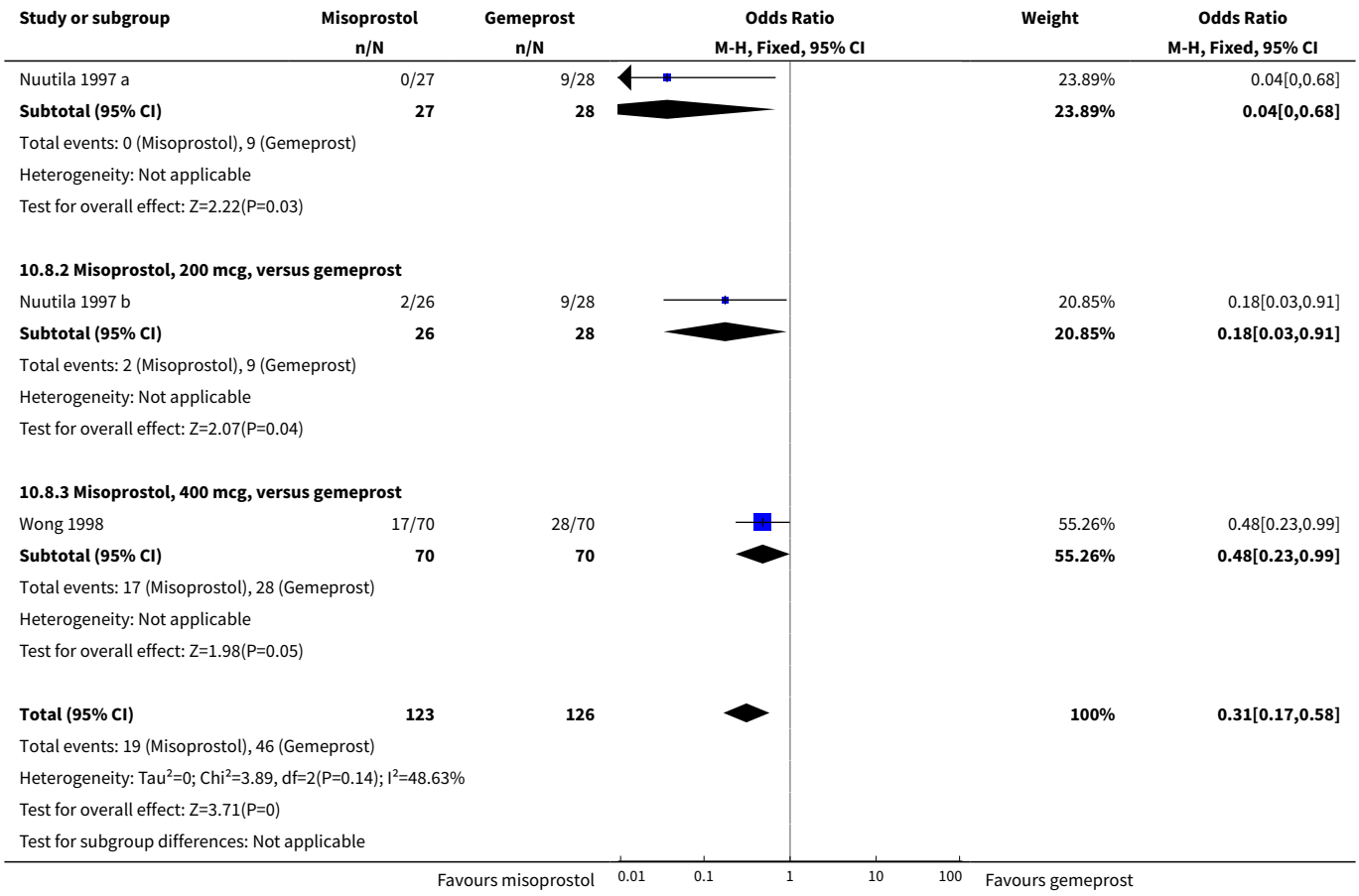


Analysis 10.7. Comparison 10 Comparison: misoprostol versus gemeprost, Outcome 7 Vomiting.



Analysis 10.8. Comparison 10 Comparison: misoprostol versus gemeprost, Outcome 8 Diarrhoea.

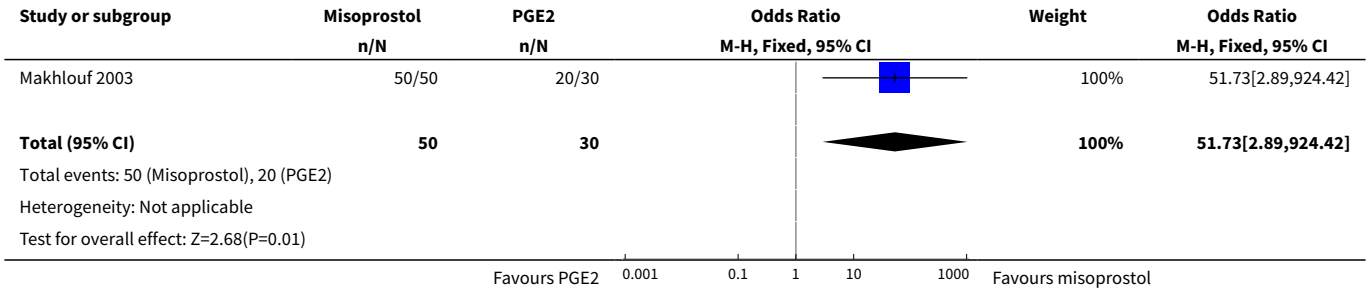




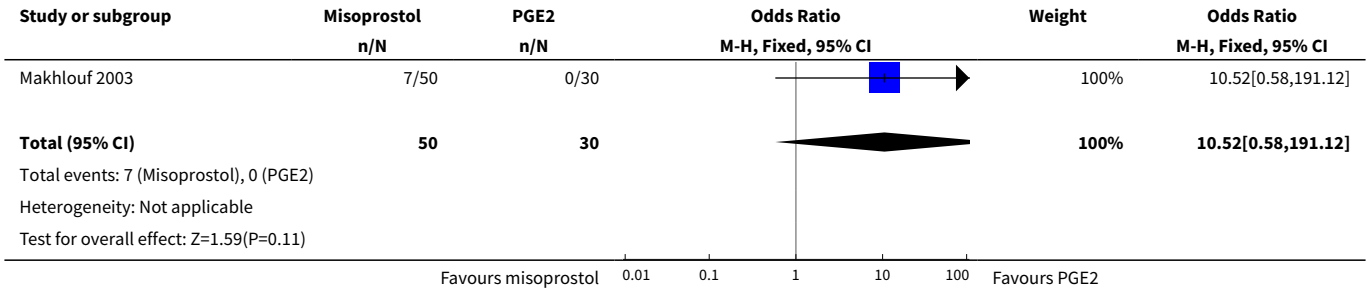
Comparison 11. Comparison: misoprostol versus dinoprost

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abortion within 24 hours	1	80	Odds Ratio (M-H, Fixed, 95% CI)	51.73 [2.89, 924.42]
2 Blood loss	1	80	Odds Ratio (M-H, Fixed, 95% CI)	10.52 [0.58, 191.12]
3 Surgical evacuation	1	80	Odds Ratio (M-H, Fixed, 95% CI)	5.90 [0.31, 113.60]
4 Pain (need analgesia)	1	80	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [0.59, 4.08]
5 Vomiting	1	80	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.52, 3.85]
6 Diarrhoea	1	80	Odds Ratio (M-H, Fixed, 95% CI)	1.85 [0.07, 46.83]

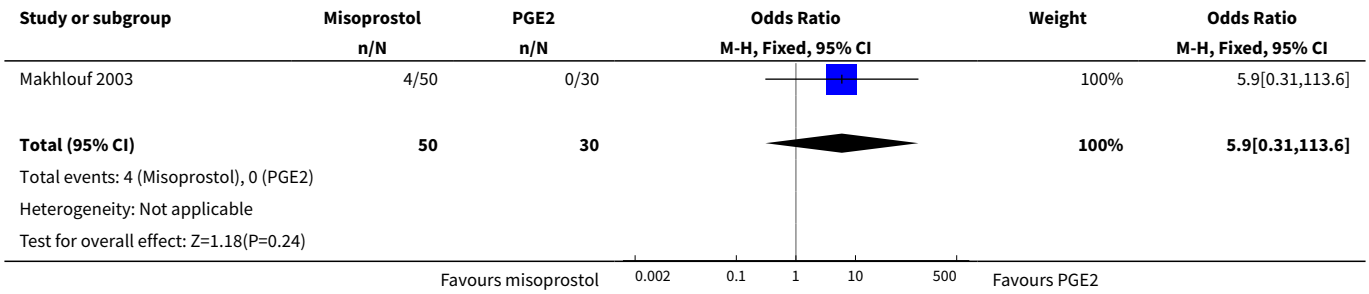
Analysis 11.1. Comparison 11 Comparison: misoprostol versus dinoprost, Outcome 1 Abortion within 24 hours.



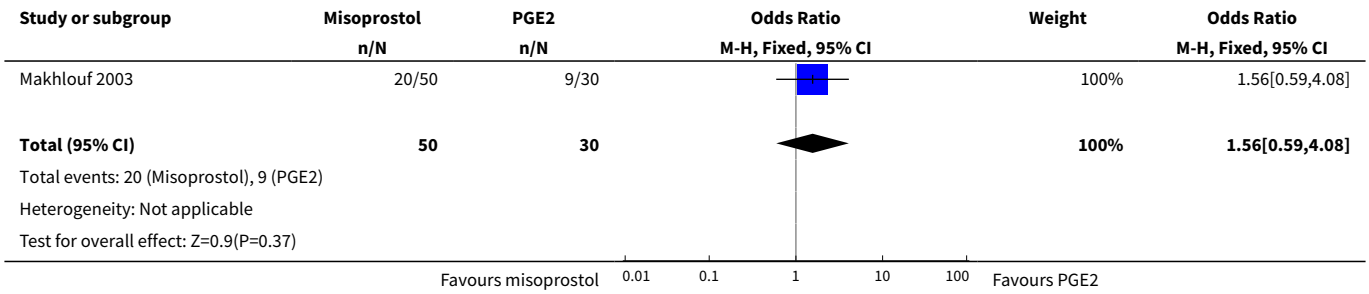
Analysis 11.2. Comparison 11 Comparison: misoprostol versus dinoprost, Outcome 2 Blood loss.



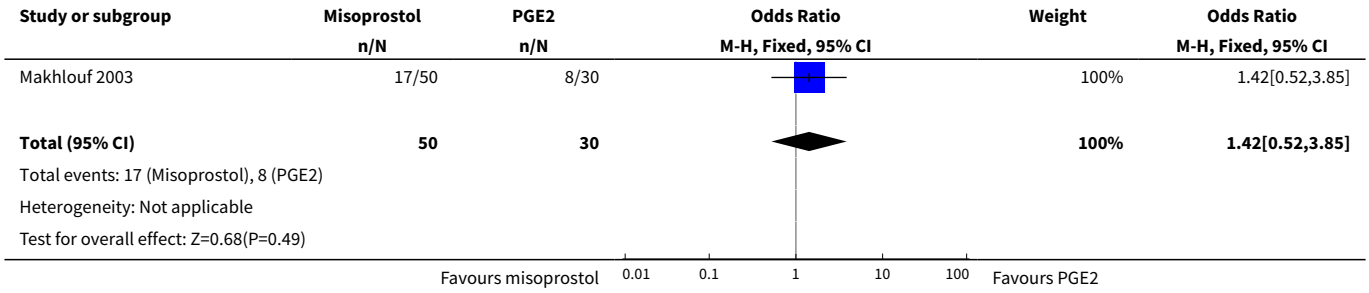
Analysis 11.3. Comparison 11 Comparison: misoprostol versus dinoprost, Outcome 3 Surgical evacuation.



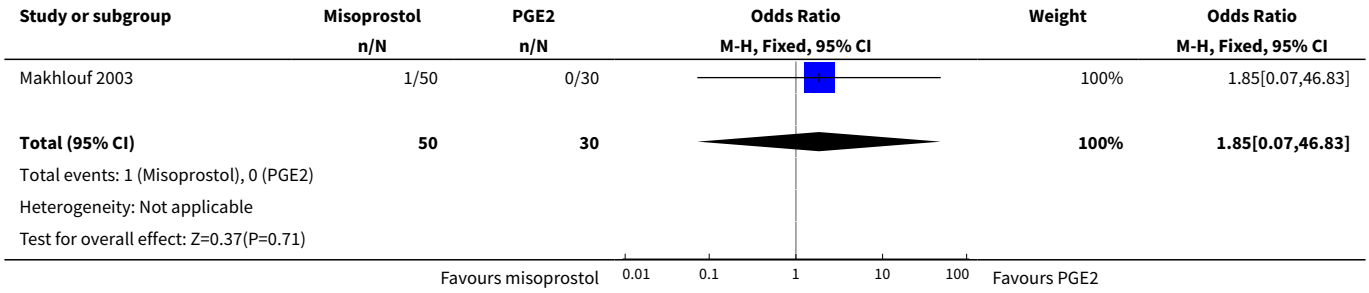
Analysis 11.4. Comparison 11 Comparison: misoprostol versus dinoprost, Outcome 4 Pain (need analgesia).



Analysis 11.5. Comparison 11 Comparison: misoprostol versus dinoprost, Outcome 5 Vomiting.



Analysis 11.6. Comparison 11 Comparison: misoprostol versus dinoprost, Outcome 6 Diarrhoea.



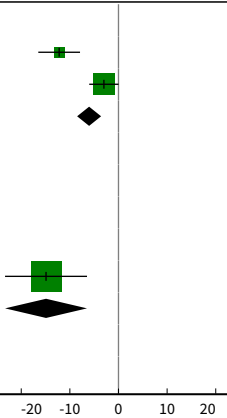
Comparison 12. Comparison: misoprostol, vaginal versus oral

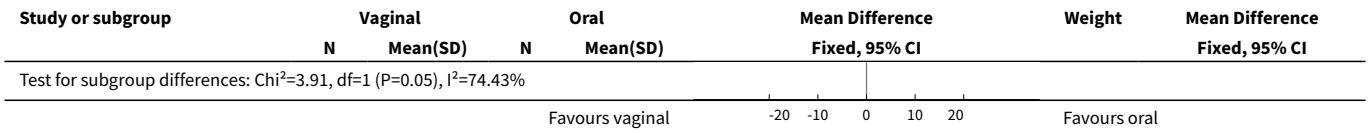
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Misoprostol 400 mcg vaginal versus 400 mcg oral	2	196	Mean Difference (IV, Fixed, 95% CI)	-6.04 [-8.51, -3.58]
1.2 Misoprostol, 400 mcg vaginal versus 200 mcg oral	1	114	Mean Difference (IV, Fixed, 95% CI)	-14.9 [-23.33, -6.47]
2 Abortion within 24 hours	1	114	Odds Ratio (M-H, Fixed, 95% CI)	9.6 [3.74, 24.66]
2.1 Misoprostol 400 mcg vaginal versus 200 mcg oral	1	114	Odds Ratio (M-H, Fixed, 95% CI)	9.6 [3.74, 24.66]
3 Blood loss (mL)	1	114	Mean Difference (IV, Fixed, 95% CI)	24.00 [-70.90, 118.90]
3.1 Misoprostol 400 mcg vaginal versus 200 mcg oral	1	114	Mean Difference (IV, Fixed, 95% CI)	24.00 [-70.90, 118.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Pain	1	108	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.08, 1.07]
4.1 Misoprostol 400 mcg vaginal versus 400 mcg oral	1	108	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.08, 1.07]
5 Surgical evacuation	3	310	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.34, 1.17]
5.1 Misoprostol 400 mcg vaginal versus 400 mcg oral	2	196	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.30, 1.21]
5.2 Misoprostol 400 mcg vaginal versus 200 mcg oral	1	114	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.20, 2.67]
6 Nausea	1	108	Odds Ratio (M-H, Fixed, 95% CI)	0.41 [0.18, 0.93]
6.1 Misoprostol 400 mcg vaginal versus 400 mcg oral	1	108	Odds Ratio (M-H, Fixed, 95% CI)	0.41 [0.18, 0.93]
7 Vomiting	1	108	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.19, 0.98]
7.1 Misoprostol 400 mcg vaginal versus 400 mcg oral	1	108	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.19, 0.98]
8 Diarrhoea	1	108	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.39, 3.85]
8.1 Misoprostol 400 mcg vaginal versus 400 mcg oral	1	108	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.39, 3.85]

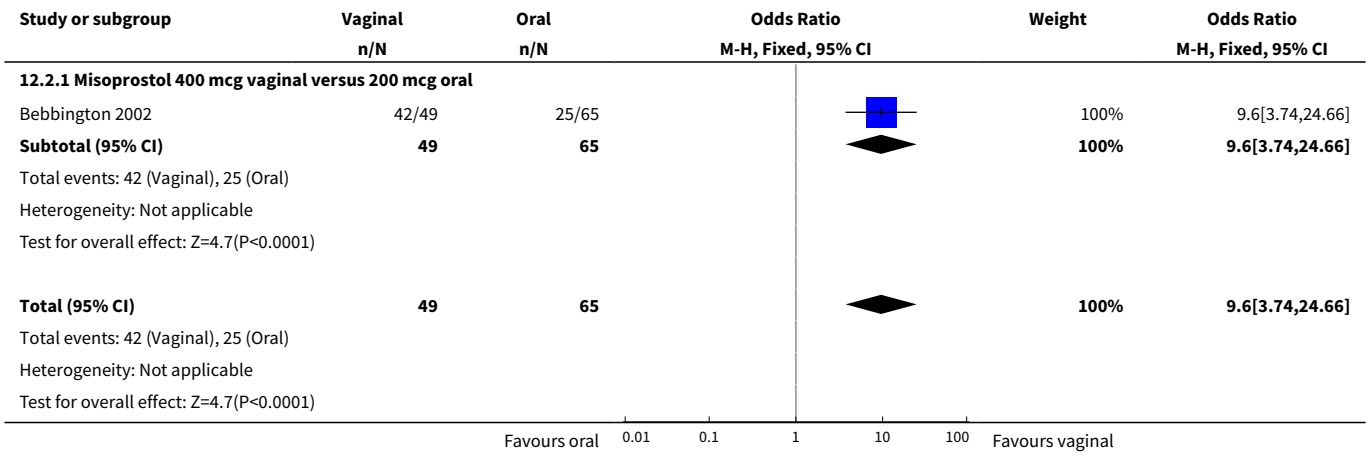
Analysis 12.1. Comparison 12 Comparison: misoprostol, vaginal versus oral, Outcome 1 Induction to abortion interval.

Study or subgroup	Vaginal N	Vaginal Mean(SD)	Oral N	Oral Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
12.1.1 Misoprostol 400 mcg vaginal versus 400 mcg oral							
Akoury 2004	84	18.3 (8.2)	52	30.5 (14.4)		33.06%	-12.2[-16.49,-7.91]
Behrashi 2008	30	9.7 (4.2)	30	12.7 (7.3)		66.94%	-3[-6.01,0.01]
Subtotal ***	**114**		**82**			**100%**	**-6.04[-8.51,-3.58]**
Heterogeneity: Tau^2=0; Chi^2=11.83, df=1(P=0); I^2=91.55%							
Test for overall effect: Z=4.8(P<0.0001)							
12.1.2 Misoprostol, 400 mcg vaginal versus 200 mcg oral							
Bebbington 2002	49	19.6 (17.5)	65	34.5 (28.2)		100%	-14.9[-23.33,-6.47]
Subtotal ***	**49**		**65**			**100%**	**-14.9[-23.33,-6.47]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=3.47(P=0)							

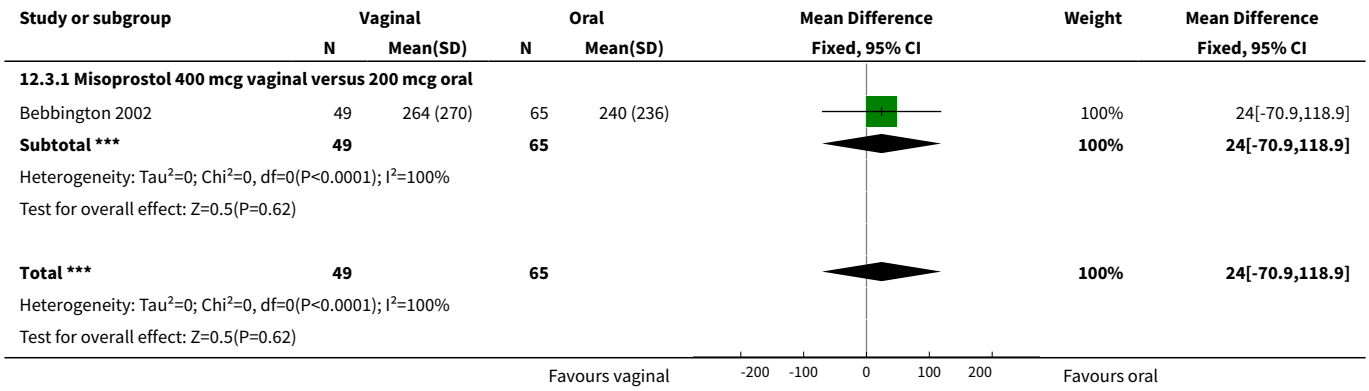




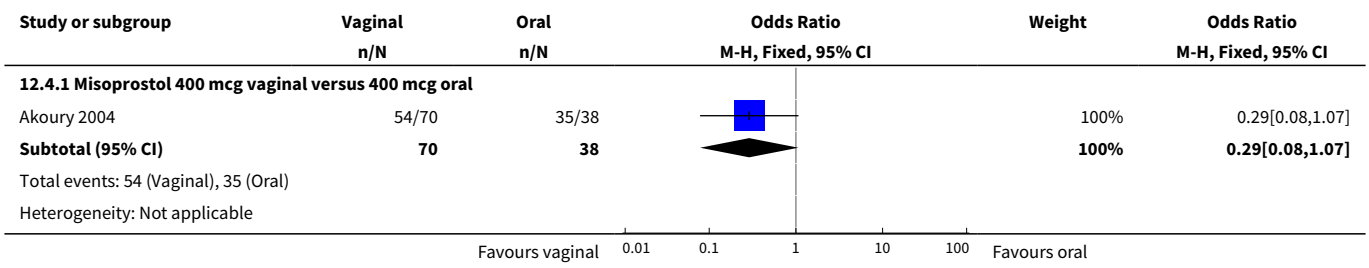
Analysis 12.2. Comparison 12 Comparison: misoprostol, vaginal versus oral, Outcome 2 Abortion within 24 hours.

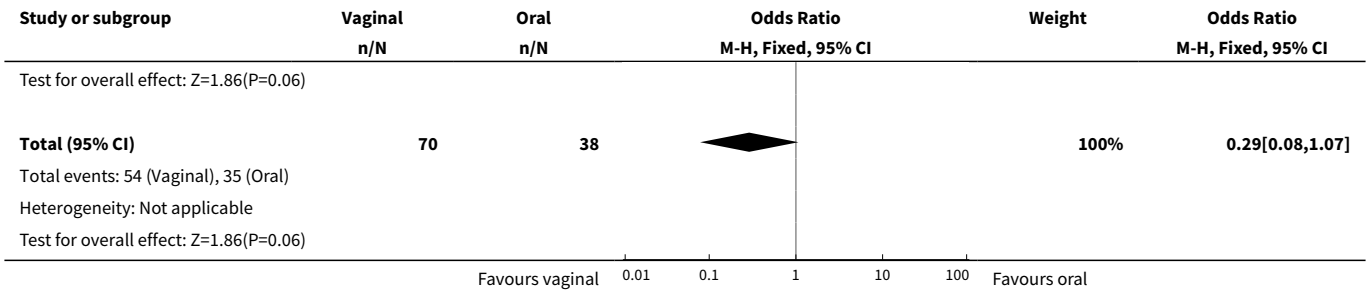


Analysis 12.3. Comparison 12 Comparison: misoprostol, vaginal versus oral, Outcome 3 Blood loss (mL).

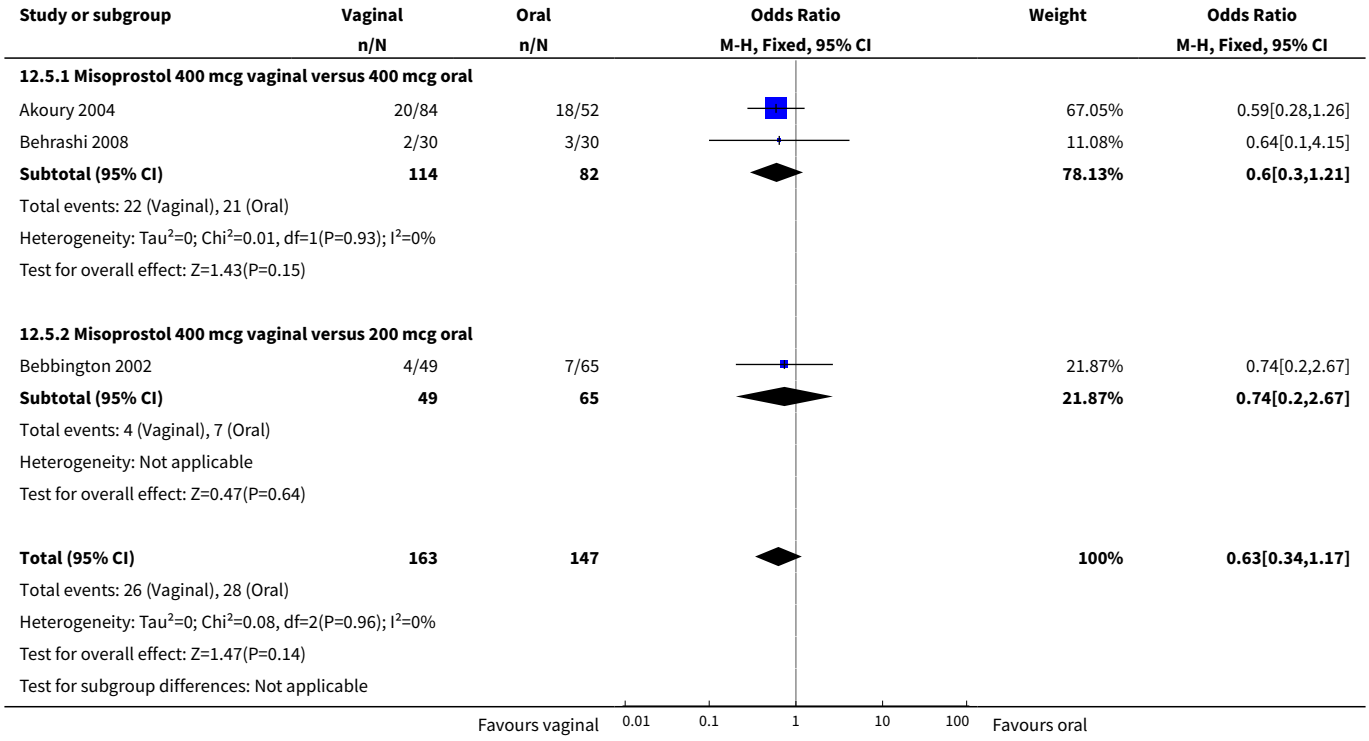


Analysis 12.4. Comparison 12 Comparison: misoprostol, vaginal versus oral, Outcome 4 Pain.

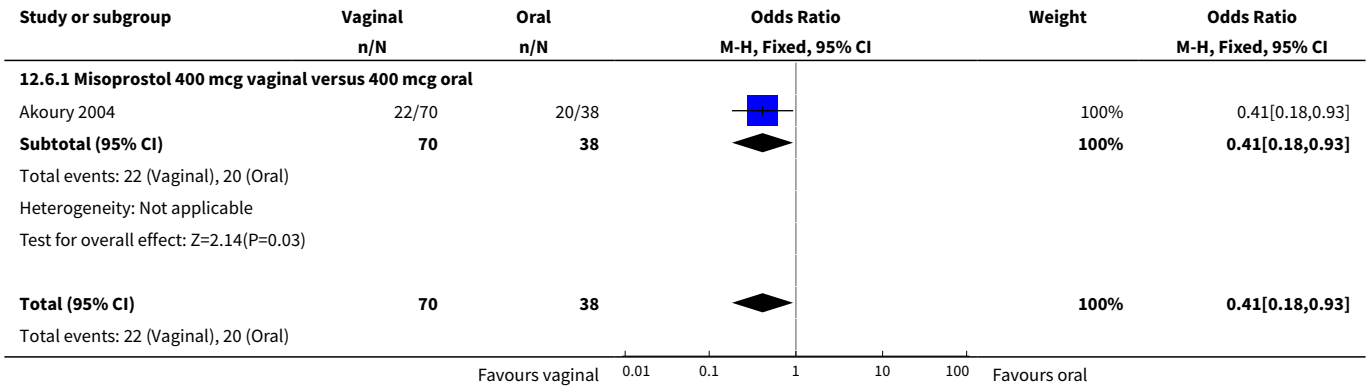


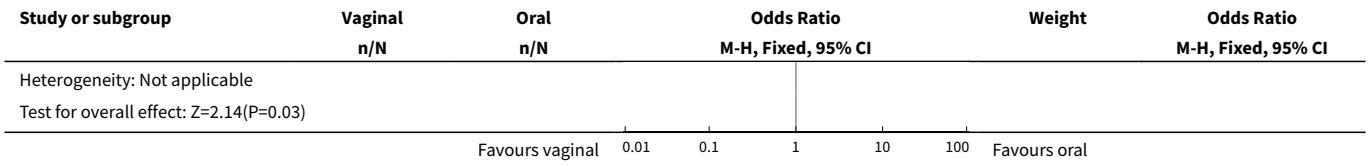


Analysis 12.5. Comparison 12 Comparison: misoprostol, vaginal versus oral, Outcome 5 Surgical evacuation.

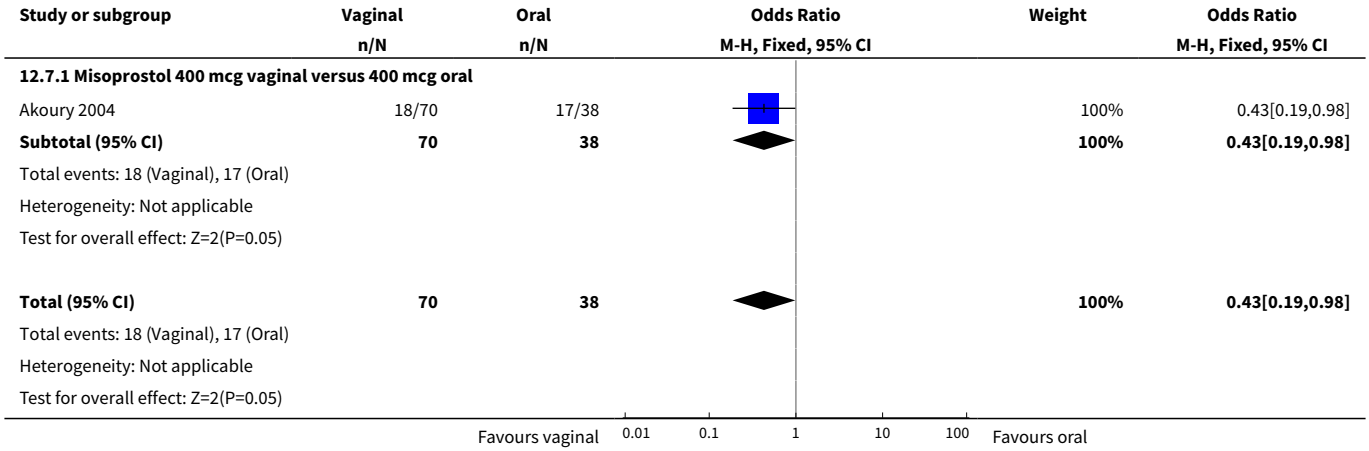


Analysis 12.6. Comparison 12 Comparison: misoprostol, vaginal versus oral, Outcome 6 Nausea.

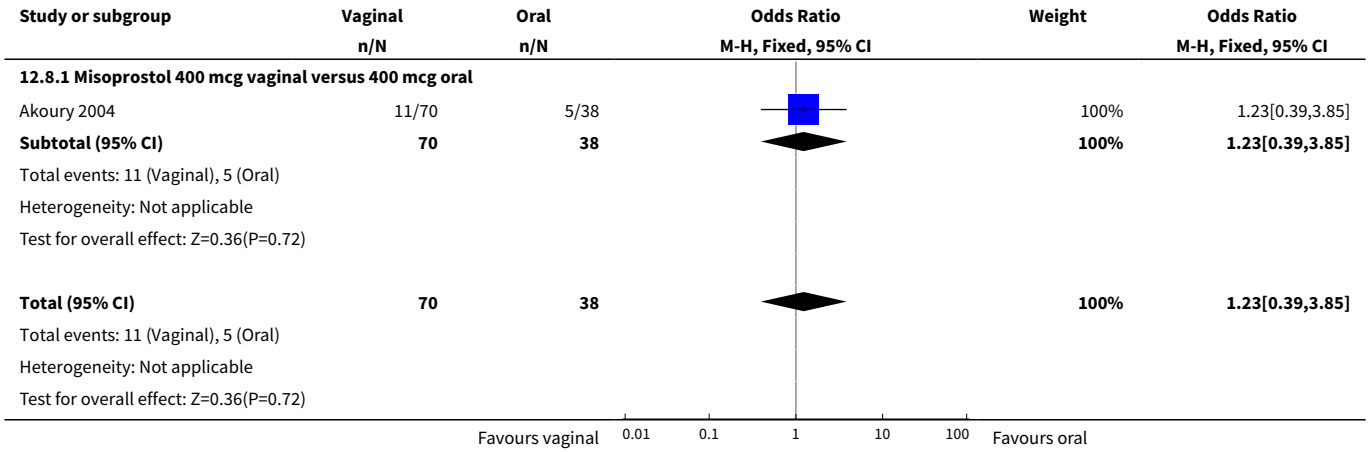




Analysis 12.7. Comparison 12 Comparison: misoprostol, vaginal versus oral, Outcome 7 Vomiting.



Analysis 12.8. Comparison 12 Comparison: misoprostol, vaginal versus oral, Outcome 8 Diarrhoea.



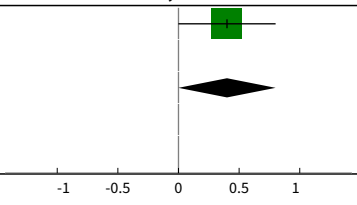
Comparison 13. Comparison: misoprostol, vaginal versus sublingual

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	1	277	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.00, 0.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Abortion within 24 hours	3	1178	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [1.05, 1.83]
3 Blood loss	1	277	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [0.52, 6.31]
4 Pain	2	497	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.73, 1.63]
5 Surgical evacuation	2	497	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.52, 1.58]
6 Nausea	3	1178	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.81, 1.48]
7 Vomiting	2	958	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.55, 1.30]
8 Diarrhoea	3	1178	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.25]

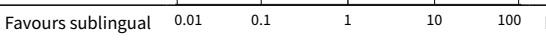
Analysis 13.1. Comparison 13 Comparison: misoprostol, vaginal versus sublingual, Outcome 1 Induction to abortion interval.

Study or subgroup	Vaginal N	Vaginal Mean(SD)	Sublingual N	Sublingual Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bhattacharjee 2008	138	14.5 (1.6)	139	14.1 (1.8)		100%	0.4[-0,0.8]
Total ***	**138**		**139**			**100%**	**0.4[-0,0.8]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.96(P=0.05)							

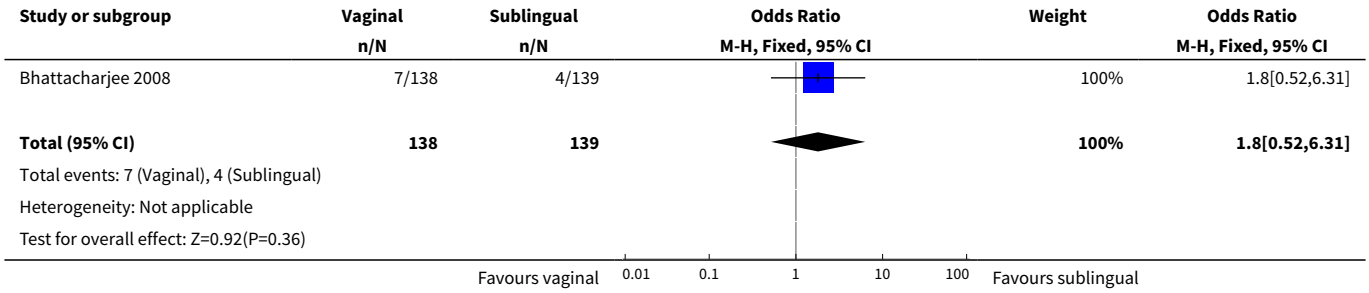


Analysis 13.2. Comparison 13 Comparison: misoprostol, vaginal versus sublingual, Outcome 2 Abortion within 24 hours.

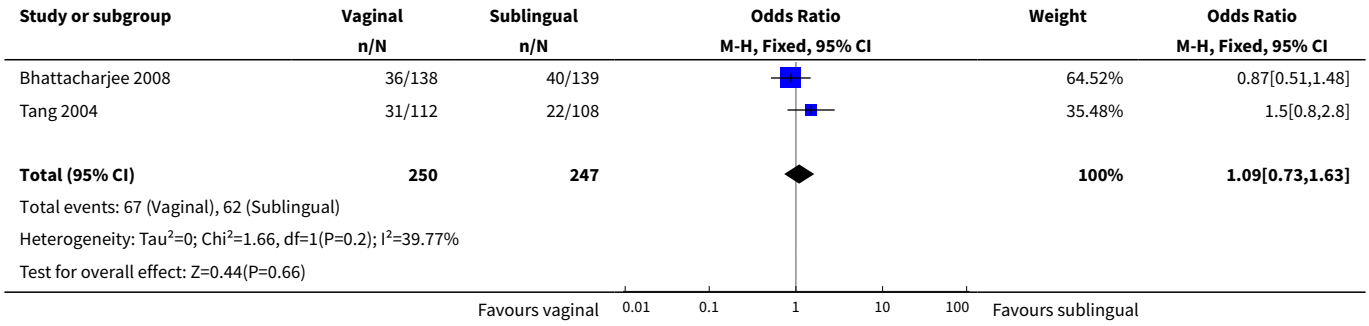
Study or subgroup	Vaginal n/N	Sublingual n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bhattacharjee 2008	85/138	89/139		40.67%	0.9[0.55,1.47]
Tang 2004	96/112	78/108		13.55%	2.31[1.17,4.54]
von Hertzen 2009	292/340	272/341		45.79%	1.54[1.03,2.31]
Total (95% CI)	**590**	**588**		**100%**	**1.39[1.05,1.83]**
Total events: 473 (Vaginal), 439 (Sublingual)					
Heterogeneity: Tau^2=0; Chi^2=5.45, df=2(P=0.07); I^2=63.32%					
Test for overall effect: Z=2.28(P=0.02)					



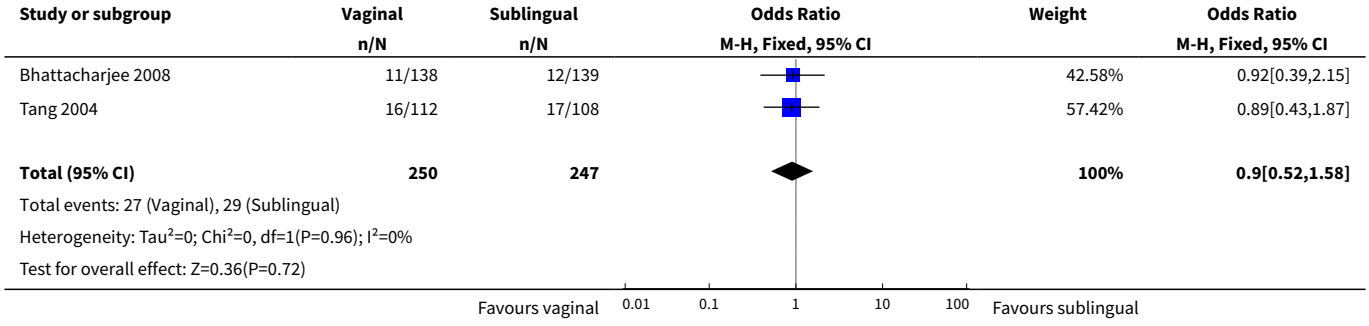
Analysis 13.3. Comparison 13 Comparison: misoprostol, vaginal versus sublingual, Outcome 3 Blood loss.



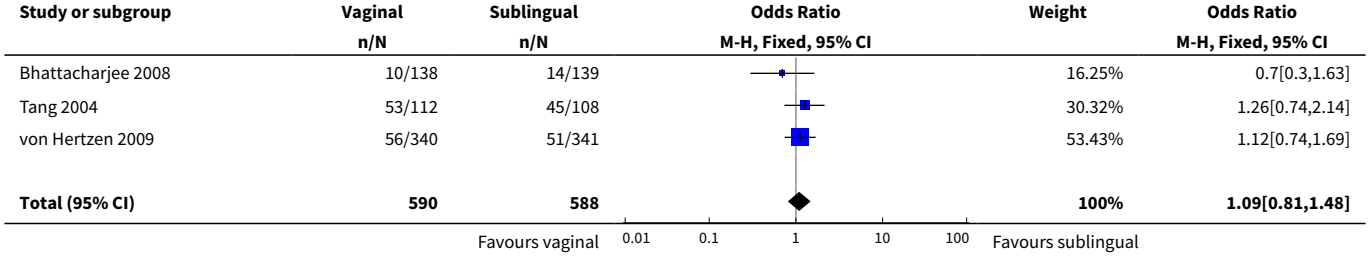
Analysis 13.4. Comparison 13 Comparison: misoprostol, vaginal versus sublingual, Outcome 4 Pain.

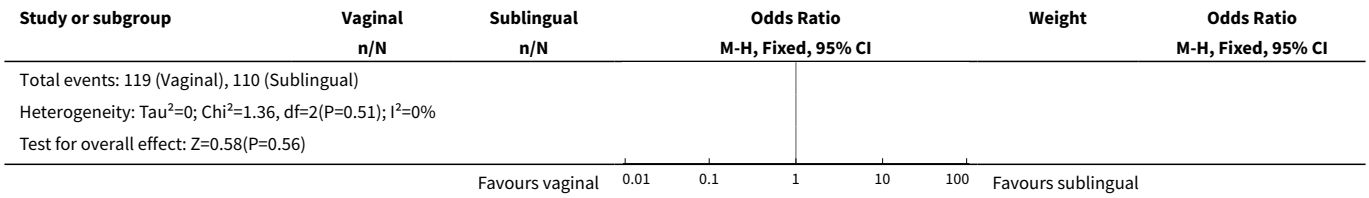


Analysis 13.5. Comparison 13 Comparison: misoprostol, vaginal versus sublingual, Outcome 5 Surgical evacuation.

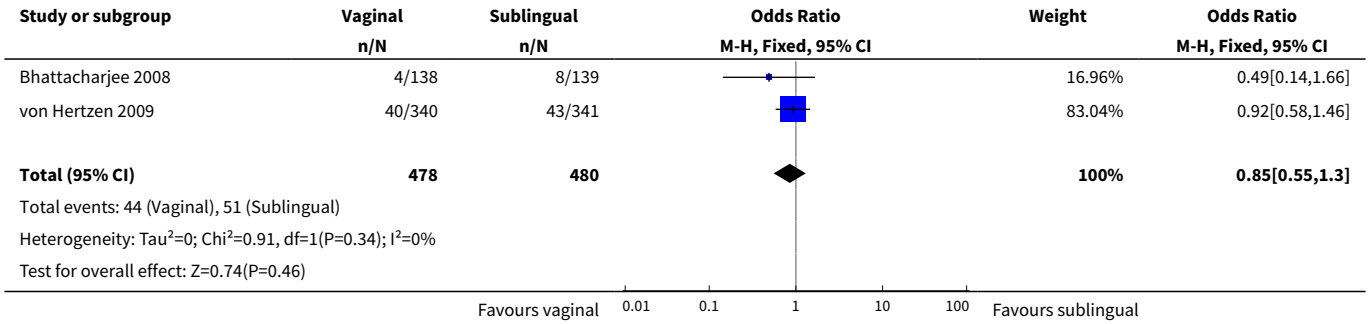


Analysis 13.6. Comparison 13 Comparison: misoprostol, vaginal versus sublingual, Outcome 6 Nausea.

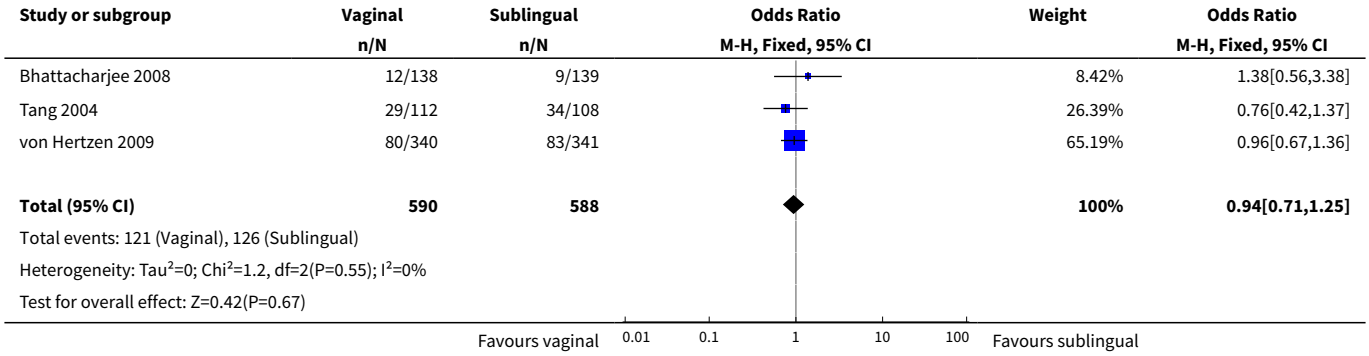




Analysis 13.7. Comparison 13 Comparison: misoprostol, vaginal versus sublingual, Outcome 7 Vomiting.



Analysis 13.8. Comparison 13 Comparison: misoprostol, vaginal versus sublingual, Outcome 8 Diarrhoea.

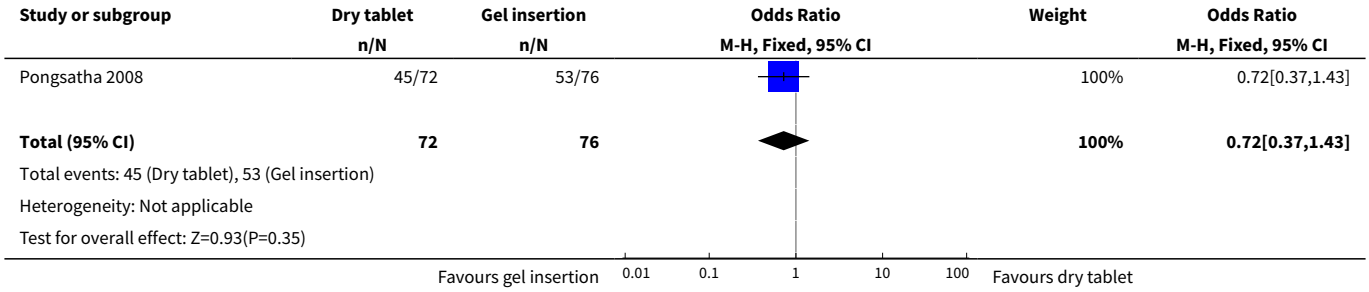


Comparison 14. Comparison: misoprostol, tablet versus gel

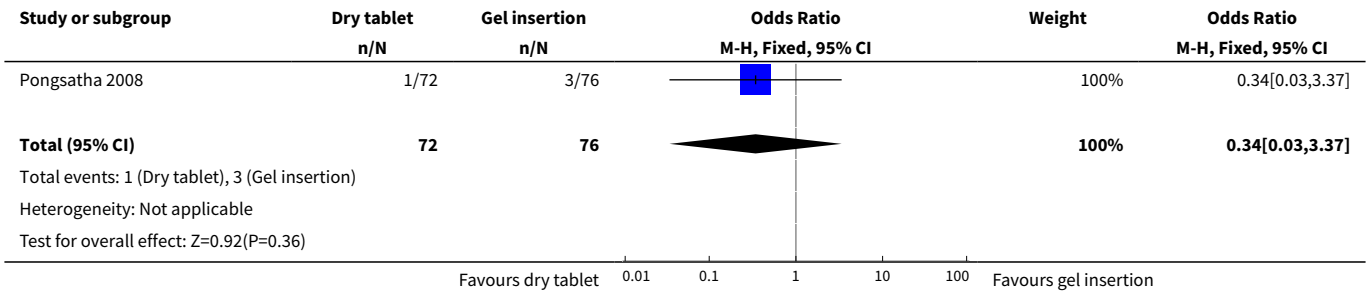
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abortion within 24 hours	1	148	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.37, 1.43]
2 Blood loss > 500 mL	1	148	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.03, 3.37]
3 Surgical evacuation	1	148	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.67, 3.15]
4 Pain	1	148	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.46, 1.93]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
5 Nausea	1	148	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [0.26, 9.92]
6 Vomiting	1	148	Odds Ratio (M-H, Fixed, 95% CI)	3.26 [0.33, 32.09]
7 Diarrhoea	1	148	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.03, 0.71]

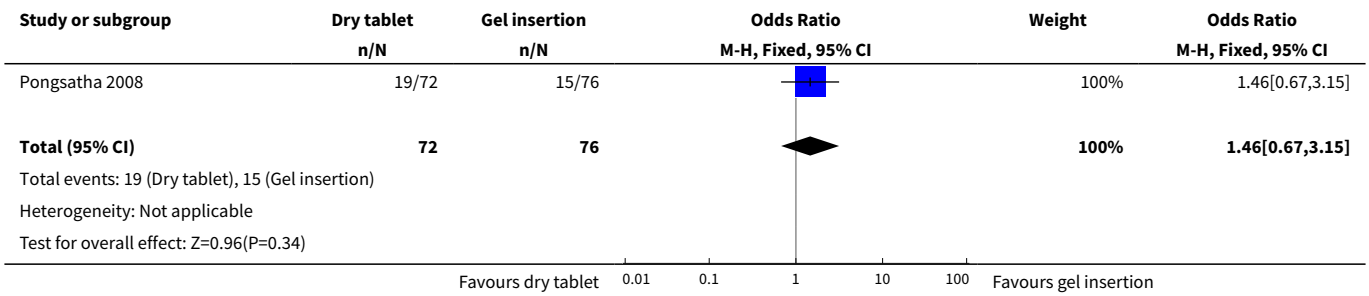
Analysis 14.1. Comparison 14 Comparison: misoprostol, tablet versus gel, Outcome 1 Abortion within 24 hours.



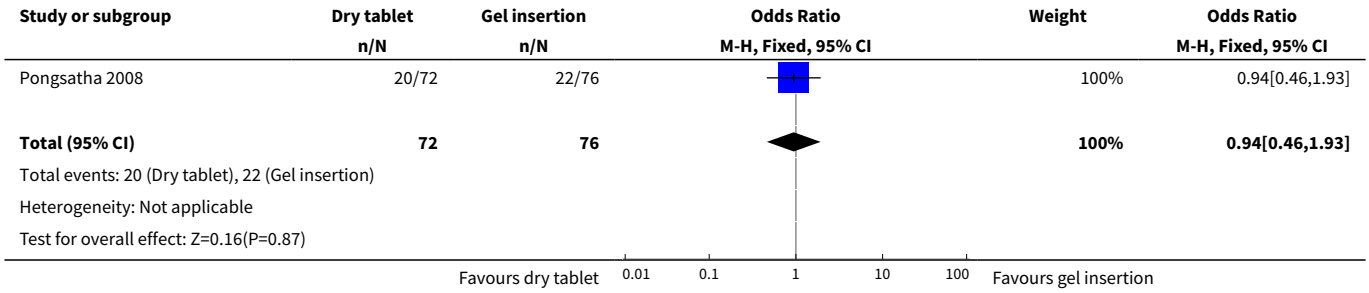
Analysis 14.2. Comparison 14 Comparison: misoprostol, tablet versus gel, Outcome 2 Blood loss > 500 mL.



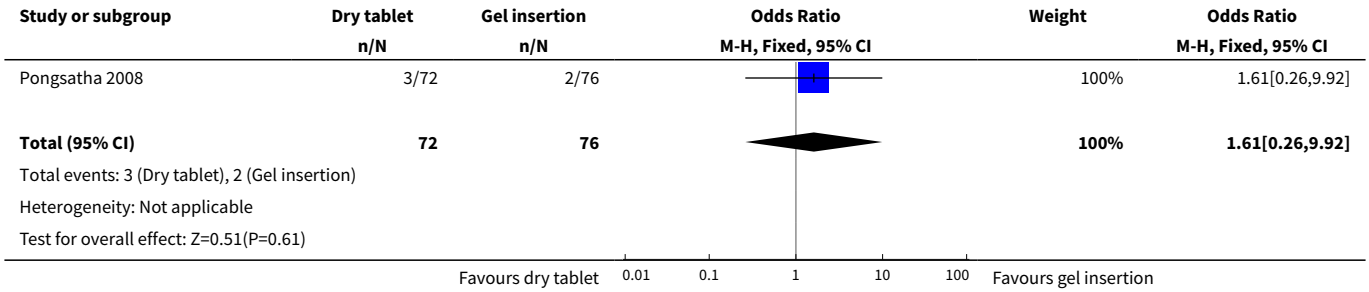
Analysis 14.3. Comparison 14 Comparison: misoprostol, tablet versus gel, Outcome 3 Surgical evacuation.



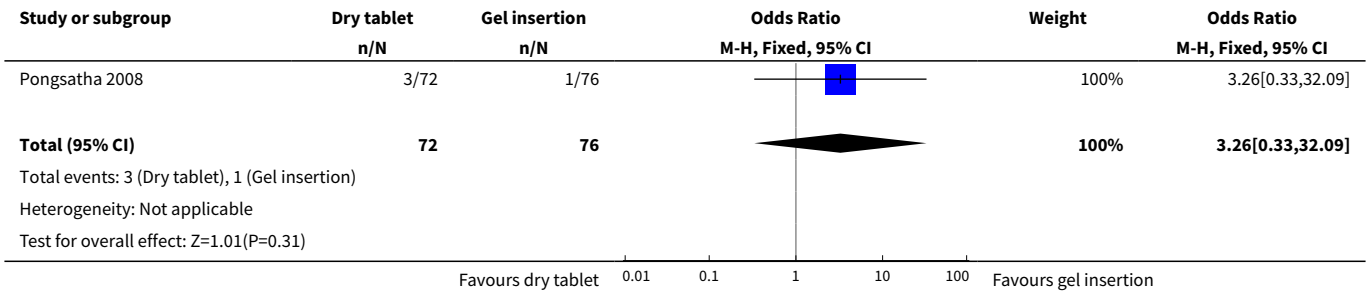
Analysis 14.4. Comparison 14 Comparison: misoprostol, tablet versus gel, Outcome 4 Pain.



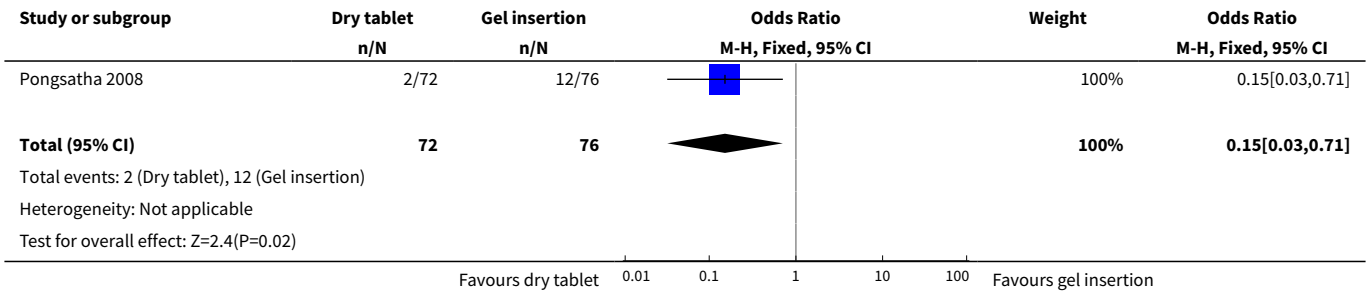
Analysis 14.5. Comparison 14 Comparison: misoprostol, tablet versus gel, Outcome 5 Nausea.



Analysis 14.6. Comparison 14 Comparison: misoprostol, tablet versus gel, Outcome 6 Vomiting.



Analysis 14.7. Comparison 14 Comparison: misoprostol, tablet versus gel, Outcome 7 Diarrhoea.

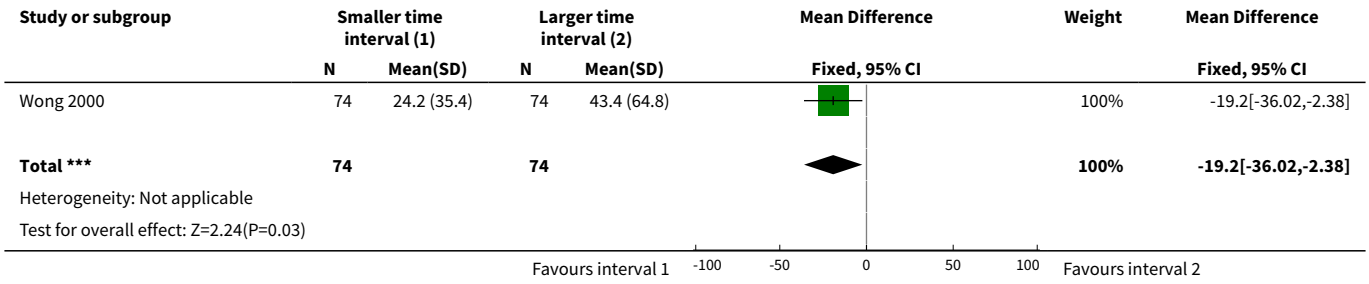


Comparison 15. Comparison: time interval misoprostol

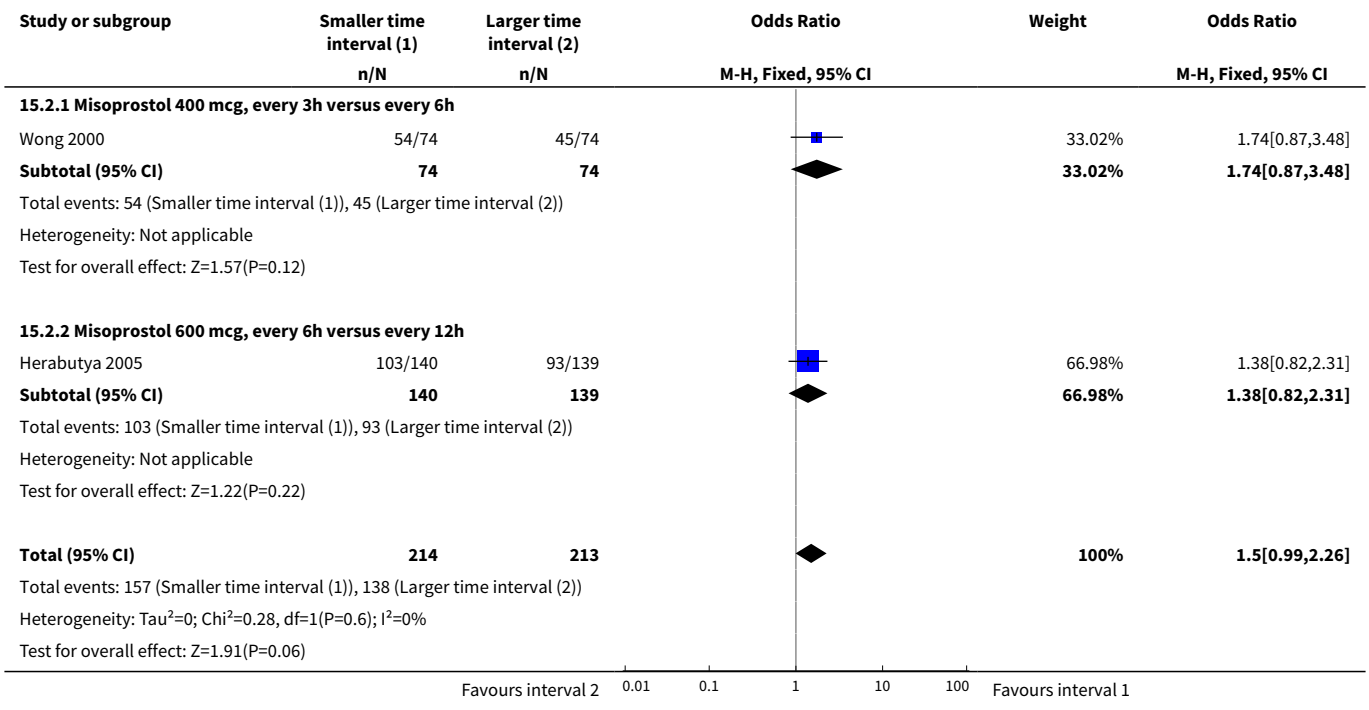
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	1	148	Mean Difference (IV, Fixed, 95% CI)	-19.2 [-36.02, -2.38]
2 Abortion within 24 hours	2	427	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.99, 2.26]
2.1 Misoprostol 400 mcg, every 3h versus every 6h	1	148	Odds Ratio (M-H, Fixed, 95% CI)	1.74 [0.87, 3.48]
2.2 Misoprostol 600 mcg, every 6h versus every 12h	1	279	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.82, 2.31]
3 Blood loss (mL)	1	148	Mean Difference (IV, Fixed, 95% CI)	-39.7 [-83.12, 3.72]
4 Blood loss (>500 mL)	1	279	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.29, 6.07]
4.1 Misoprostol 600 mcg, every 6h versus every 12h	1	279	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.29, 6.07]
5 Surgical evacuation	1	155	Odds Ratio (M-H, Fixed, 95% CI)	6.14 [0.31, 120.92]
5.1 Misoprostol 600 mcg, every 6h versus every 12h	1	155	Odds Ratio (M-H, Fixed, 95% CI)	6.14 [0.31, 120.92]
6 Pain	2	427	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.75, 1.70]
6.1 Misoprostol 400 mcg, every 3h versus every 6h	1	148	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.45, 1.74]
6.2 Misoprostol 600 mcg, every 6h versus every 12h	1	279	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.78, 2.16]
7 Nausea	2	427	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.64, 2.45]
7.1 Misoprostol 400 mcg, every 3h versus every 6h	1	148	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.27, 2.15]
7.2 Misoprostol 600 mcg, every 6h versus every 12h	1	279	Odds Ratio (M-H, Fixed, 95% CI)	1.82 [0.74, 4.49]
8 Vomiting	2	427	Odds Ratio (M-H, Fixed, 95% CI)	1.47 [0.72, 3.00]
8.1 Misoprostol 400 mcg, every 3h versus every 6h	1	148	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.35, 2.82]

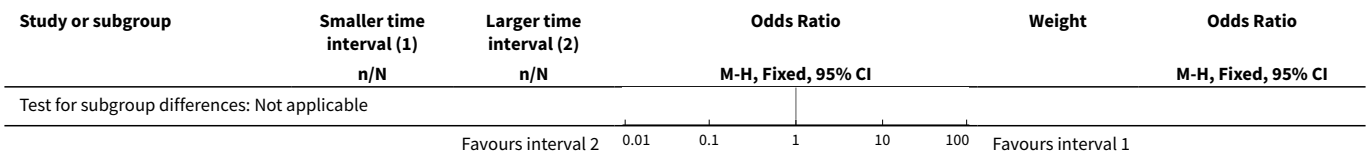
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Misoprostol 600 mcg, every 6h versus every 12h	1	279	Odds Ratio (M-H, Fixed, 95% CI)	2.08 [0.76, 5.70]
9 Diarrhoea	2	427	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.80, 2.04]
9.1 Misoprostol 400 mcg, every 3h versus every 6h	1	148	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.37, 11.59]
9.2 Misoprostol 600 mcg, every 6h versus every 12h	1	279	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.75, 2.00]

Analysis 15.1. Comparison 15 Comparison: time interval misoprostol, Outcome 1 Induction to abortion interval.

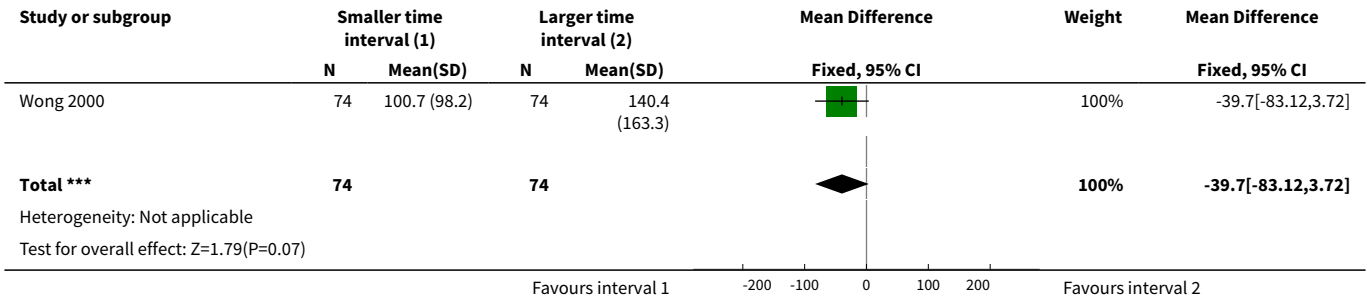


Analysis 15.2. Comparison 15 Comparison: time interval misoprostol, Outcome 2 Abortion within 24 hours.

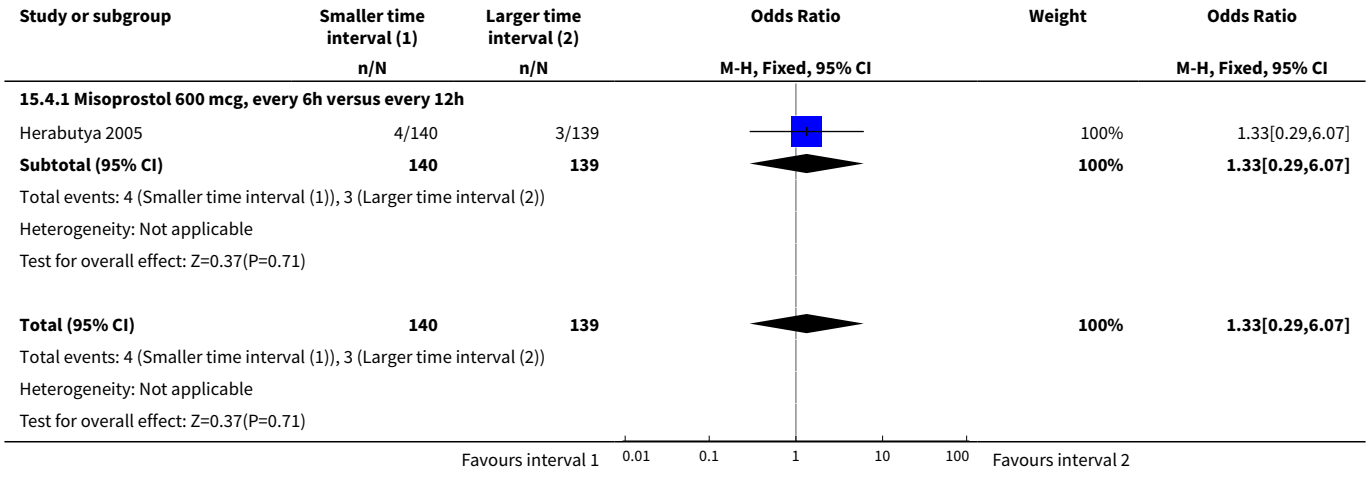




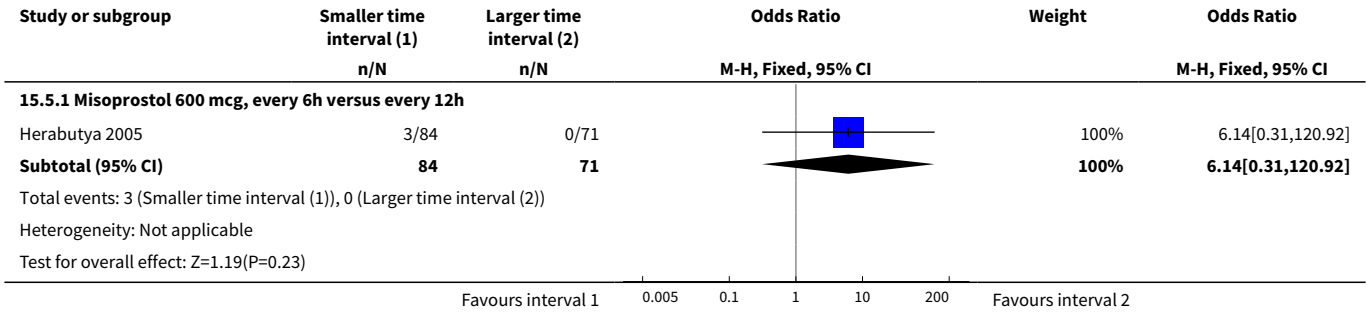
Analysis 15.3. Comparison 15 Comparison: time interval misoprostol, Outcome 3 Blood loss (mL).

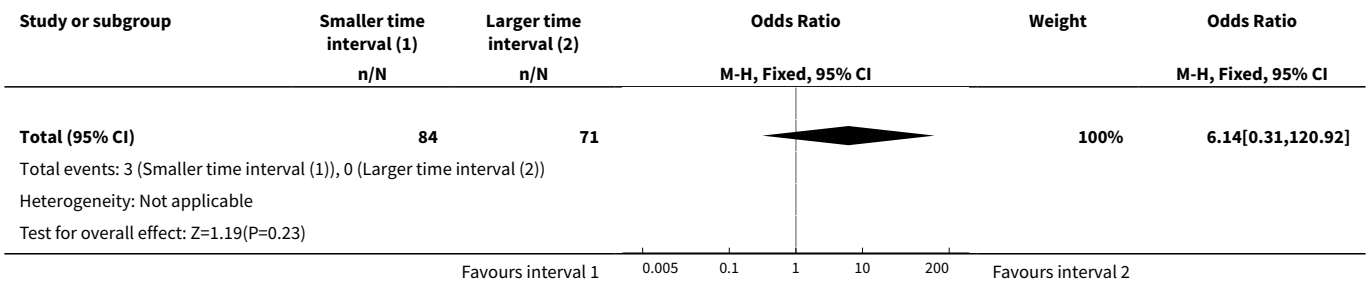


Analysis 15.4. Comparison 15 Comparison: time interval misoprostol, Outcome 4 Blood loss (>500 mL).

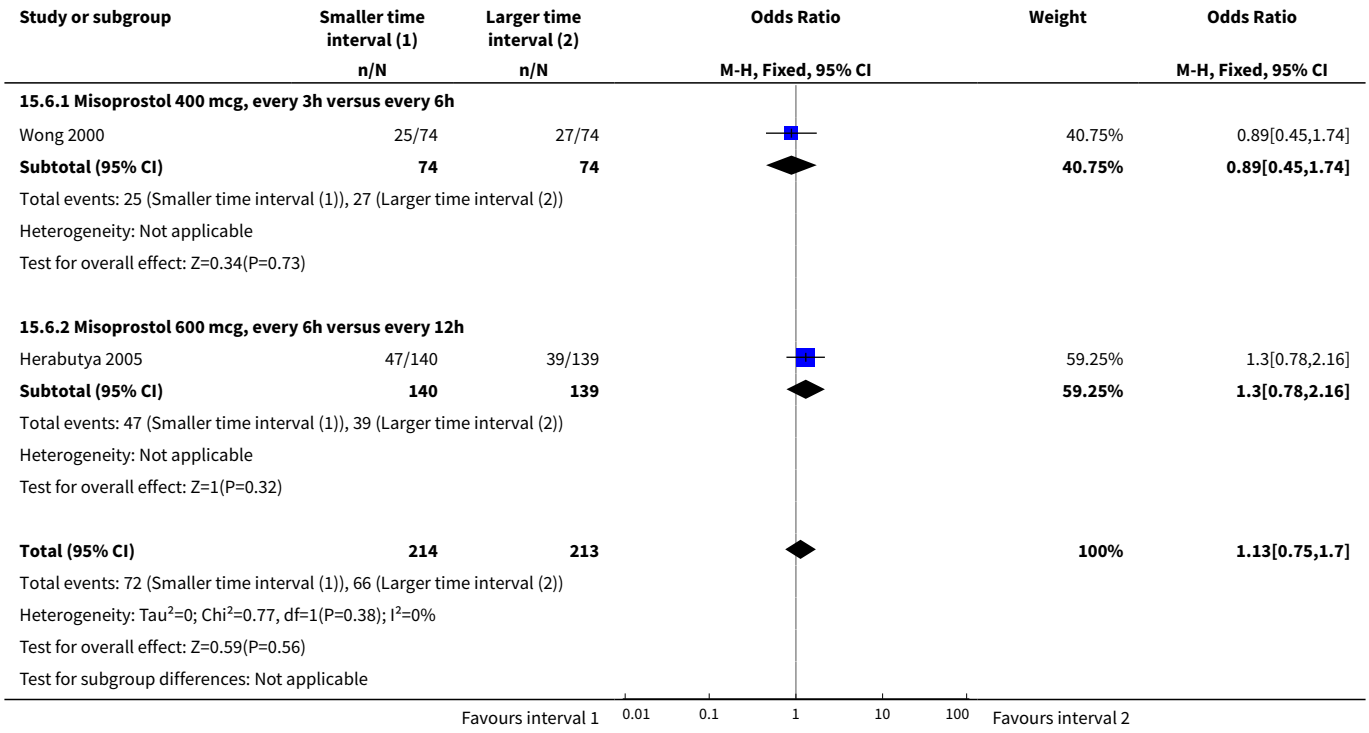


Analysis 15.5. Comparison 15 Comparison: time interval misoprostol, Outcome 5 Surgical evacuation.

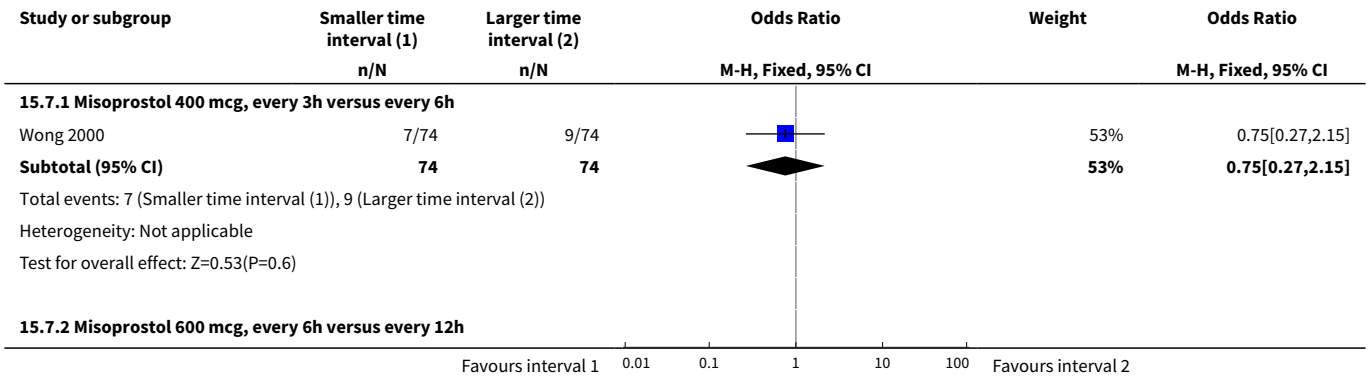


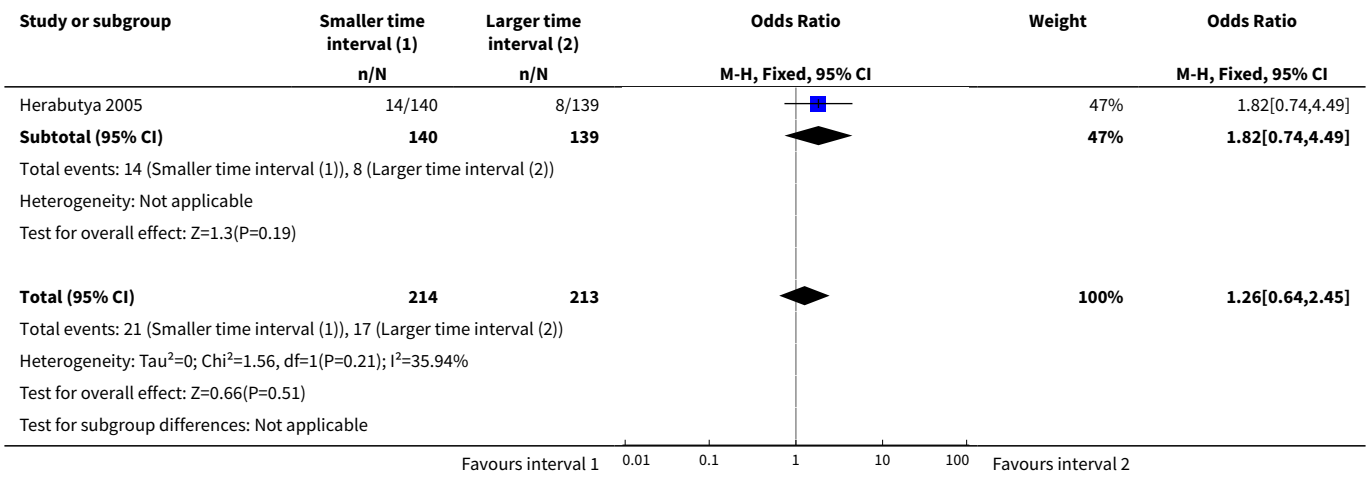


Analysis 15.6. Comparison 15 Comparison: time interval misoprostol, Outcome 6 Pain.

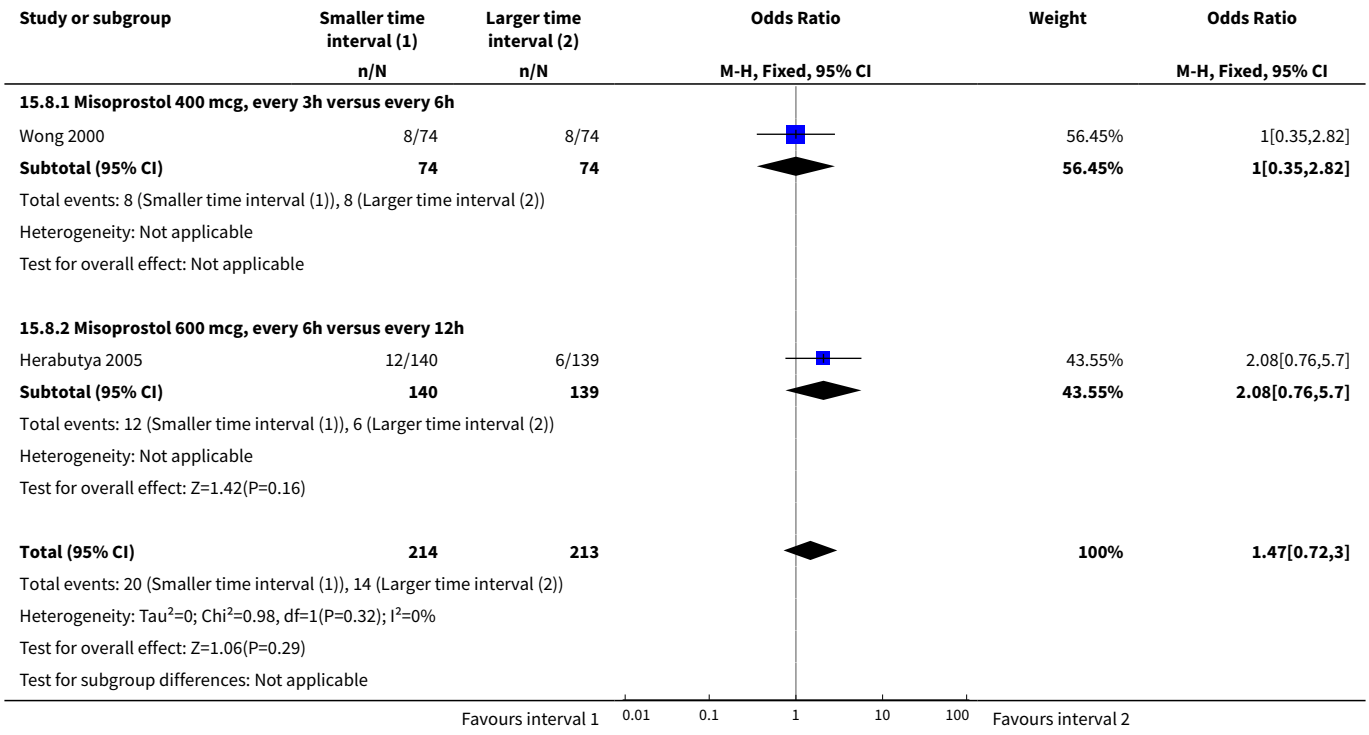


Analysis 15.7. Comparison 15 Comparison: time interval misoprostol, Outcome 7 Nausea.

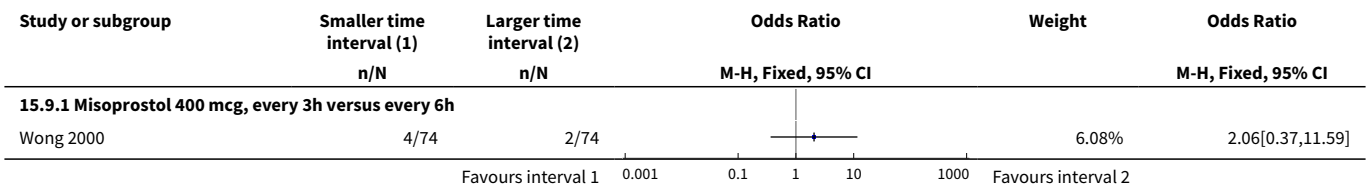


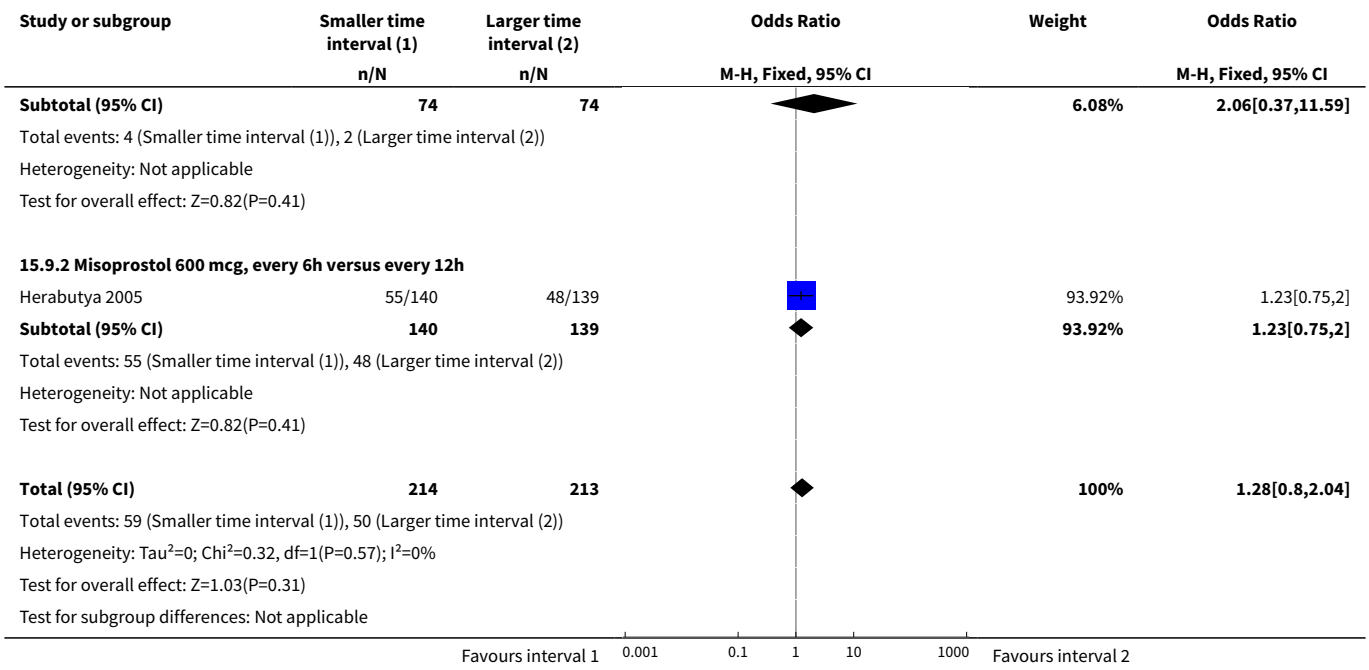


Analysis 15.8. Comparison 15 Comparison: time interval misoprostol, Outcome 8 Vomiting.



Analysis 15.9. Comparison 15 Comparison: time interval misoprostol, Outcome 9 Diarrhoea.

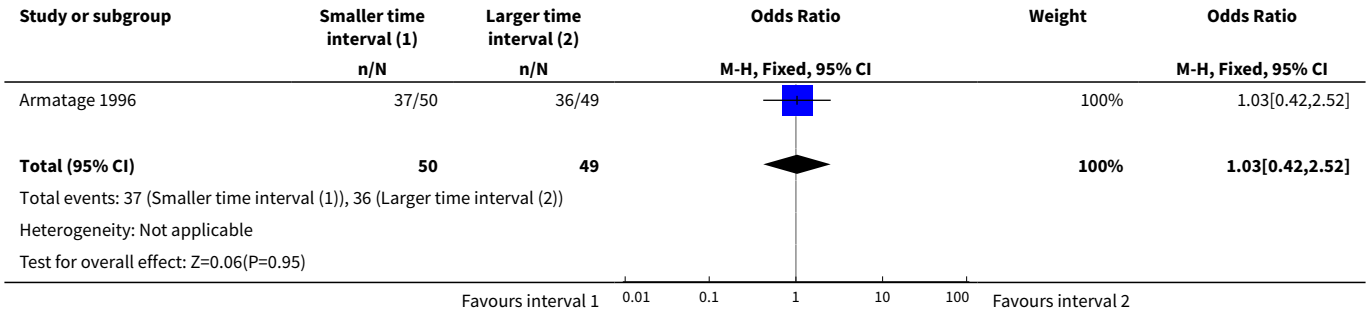




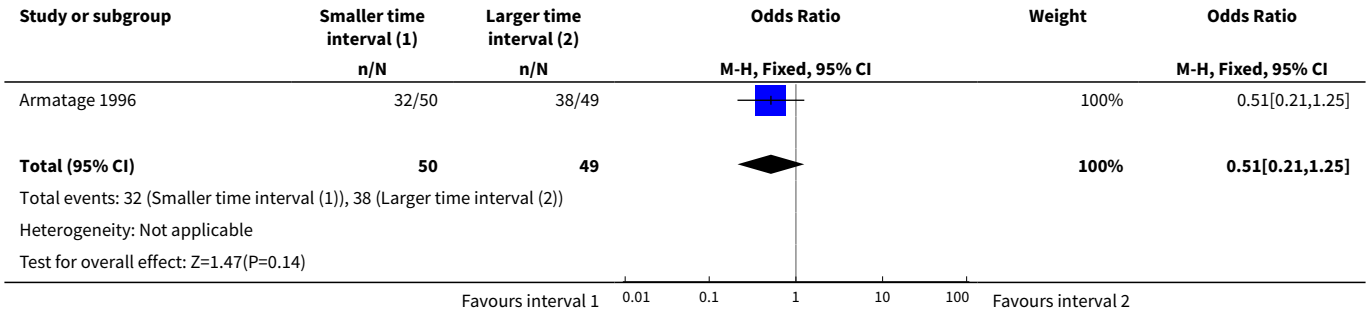
Comparison 16. Comparison: time interval gemeprost

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abortion within 24 hours	1	99	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.42, 2.52]
2 Surgical evacuations	1	99	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.21, 1.25]
3 Pain	1	99	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [0.71, 5.09]

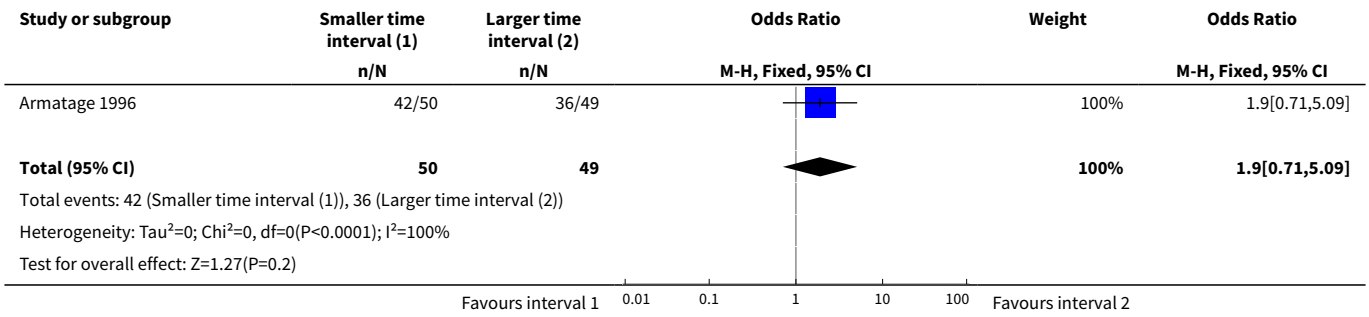
Analysis 16.1. Comparison 16 Comparison: time interval gemeprost, Outcome 1 Abortion within 24 hours.



Analysis 16.2. Comparison 16 Comparison: time interval gemeprost, Outcome 2 Surgical evacuations.



Analysis 16.3. Comparison 16 Comparison: time interval gemeprost, Outcome 3 Pain.



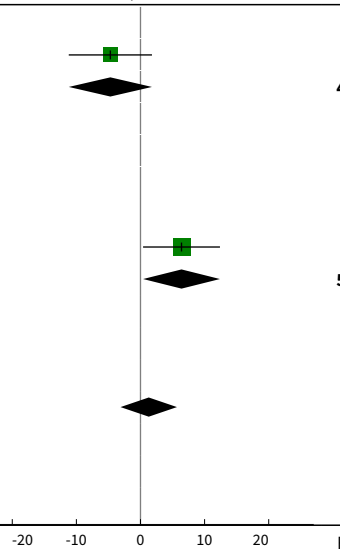
Comparison 17. Comparison: low dose versus high dose of misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	2	113	Mean Difference (IV, Fixed, 95% CI)	1.29 [-3.12, 5.69]
1.1 100 mcg versus 200 mcg	1	53	Mean Difference (IV, Fixed, 95% CI)	-4.70 [-11.19, 1.79]
1.2 400 mcg versus 600 mcg	1	60	Mean Difference (IV, Fixed, 95% CI)	6.4 [0.40, 12.40]
2 Pain	2	113	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.29, 1.95]
2.1 100 mcg versus 200 mcg	1	53	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.32, 2.75]
2.2 400 mcg versus 600 mcg	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.03, 3.17]
3 Nausea	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.10, 4.15]
3.1 400 mcg versus 600 mcg	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.10, 4.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Vomiting	2	113	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.42, 4.85]
4.1 100 mcg versus 200 mcg	1	53	Odds Ratio (M-H, Fixed, 95% CI)	2.19 [0.49, 9.88]
4.2 400 mcg versus 600 mcg	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.63]
5 Diarrhoea	2	113	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.11, 2.58]
5.1 100 mcg versus 200 mcg	1	53	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.90]
5.2 400 mcg versus 600 mcg	1	60	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.60]

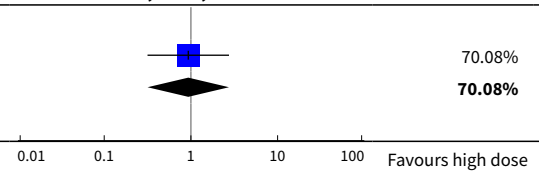
Analysis 17.1. Comparison 17 Comparison: low dose versus high dose of misoprostol, Outcome 1 Induction to abortion interval.

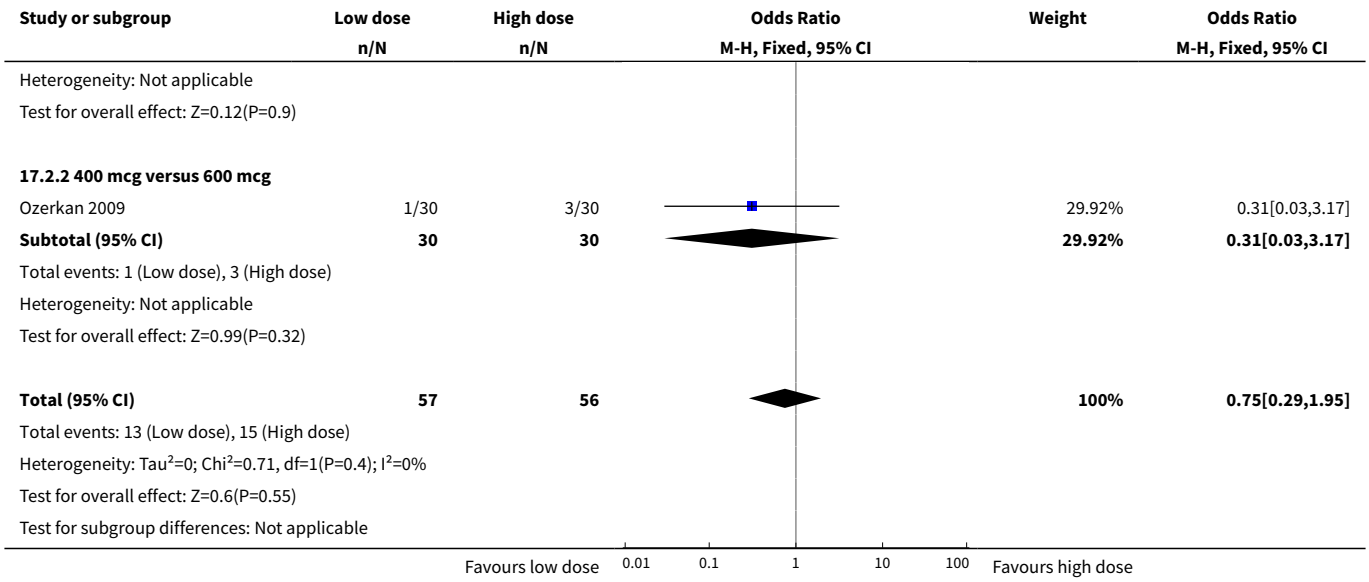
Study or subgroup	Low dose N	Low dose Mean(SD)	High dose N	High dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
17.1.1 100 mcg versus 200 mcg							
Nuutila 1997 c	27	23.1 (12.3)	26	27.8 (11.8)		46.06%	-4.7[-11.19,1.79]
Subtotal ***	**27**		**26**			**46.06%**	**-4.7[-11.19,1.79]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.42(P=0.16)							
17.1.2 400 mcg versus 600 mcg							
Ozerkan 2009	30	21.8 (13.8)	30	15.4 (9.5)		53.94%	6.4[0.4,12.4]
Subtotal ***	**30**		**30**			**53.94%**	**6.4[0.4,12.4]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.09(P=0.04)							
Total ***	**57**		**56**			**100%**	**1.29[-3.12,5.69]**
Heterogeneity: Tau^2=0; Chi^2=6.06, df=1(P=0.01); I^2=83.51%							
Test for overall effect: Z=0.57(P=0.57)							
Test for subgroup differences: Chi^2=6.06, df=1 (P=0.01), I^2=83.51%							



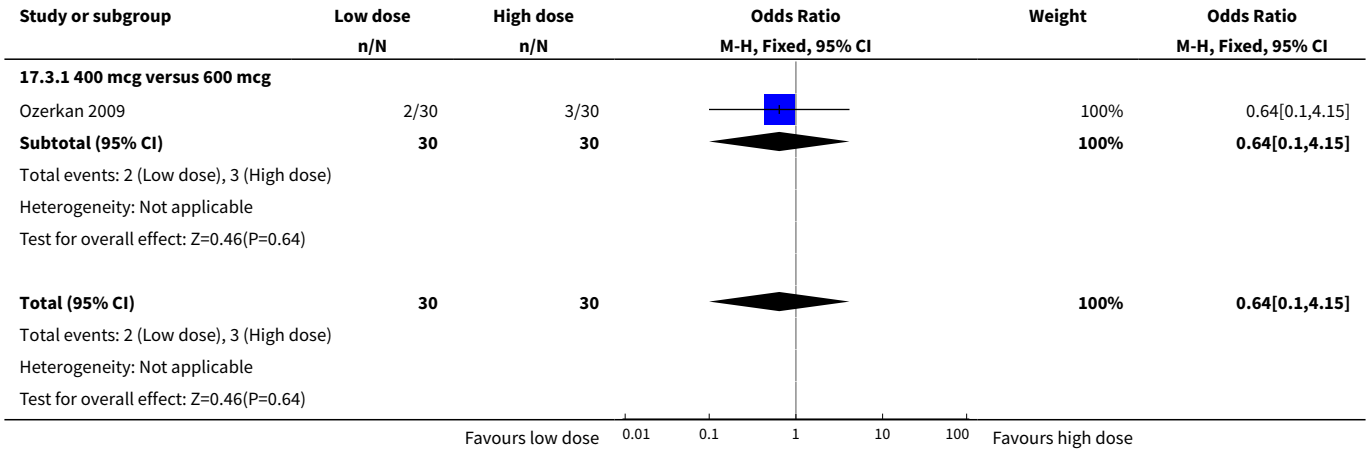
Analysis 17.2. Comparison 17 Comparison: low dose versus high dose of misoprostol, Outcome 2 Pain.

Study or subgroup	Low dose n/N	High dose n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
17.2.1 100 mcg versus 200 mcg					
Nuutila 1997 c	12/27	12/26		70.08%	0.93[0.32,2.75]
Subtotal (95% CI)	**27**	**26**		**70.08%**	**0.93[0.32,2.75]**
Total events: 12 (Low dose), 12 (High dose)					

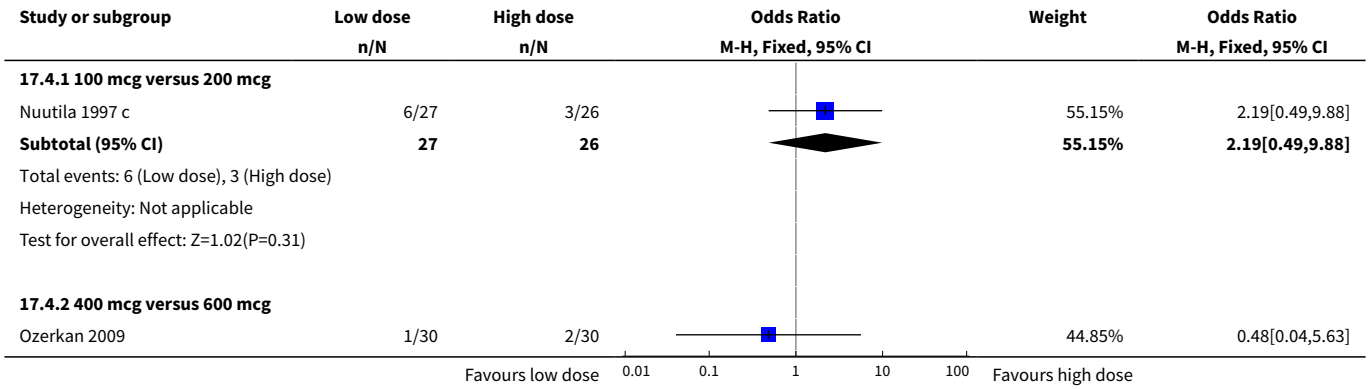


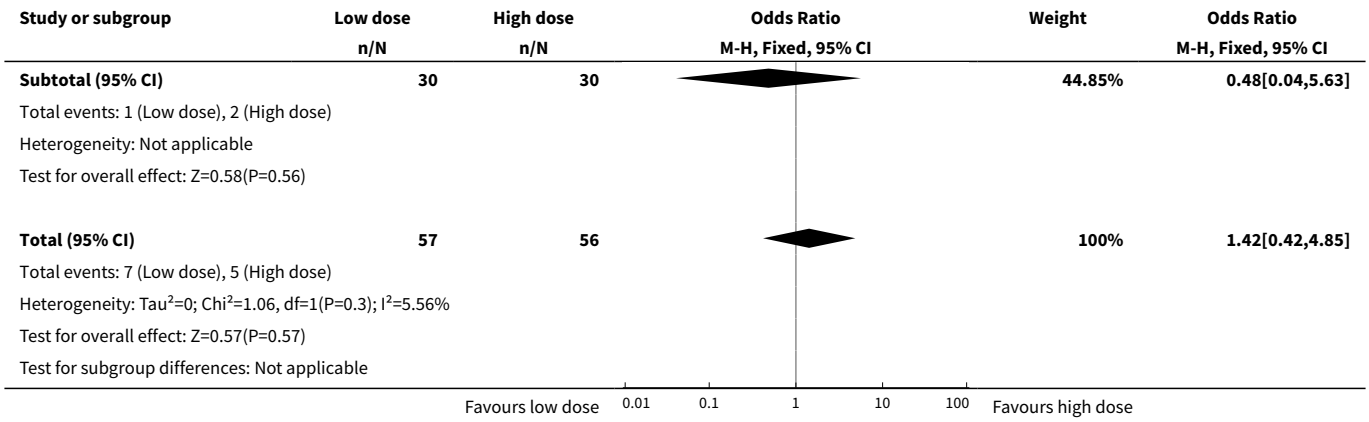


Analysis 17.3. Comparison 17 Comparison: low dose versus high dose of misoprostol, Outcome 3 Nausea.

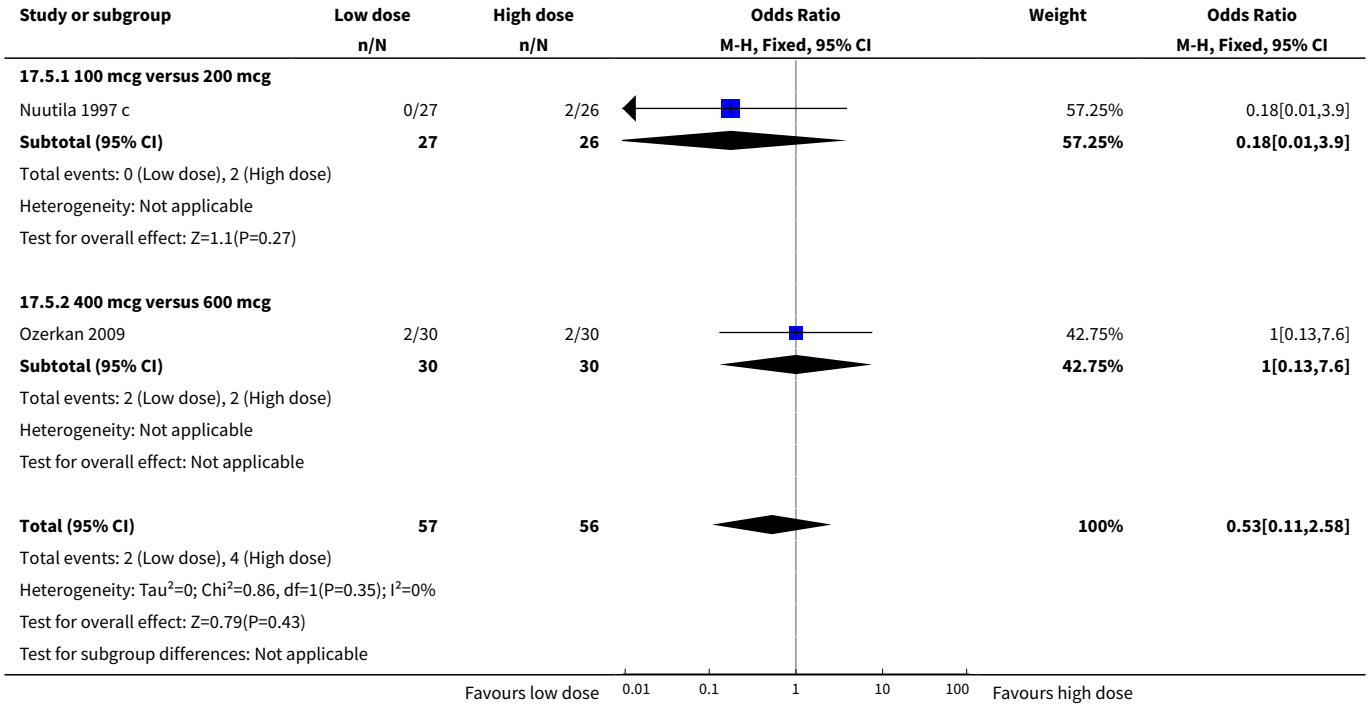


Analysis 17.4. Comparison 17 Comparison: low dose versus high dose of misoprostol, Outcome 4 Vomiting.





Analysis 17.5. Comparison 17 Comparison: low dose versus high dose of misoprostol, Outcome 5 Diarrhoea.



Comparison 18. Comparison: PGE2 versus PGF2

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	1	50	Mean Difference (IV, Fixed, 95% CI)	-9.10 [-13.68, -4.52]
2 Abortion within 24 hours	1	50	Odds Ratio (M-H, Fixed, 95% CI)	11.29 [1.29, 98.89]

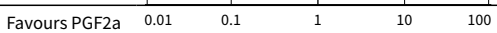
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 Pain	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.84]
4 Nausea	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.07, 1.26]
5 Vomiting	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-2.32, 0.92]
6 Diarrhoea	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-2.28, 0.68]

Analysis 18.1. Comparison 18 Comparison: PGE2 versus PGF2, Outcome 1 Induction to abortion interval.

Study or subgroup	PGE2 N	PGE2 Mean(SD)	PGF2a N	PGF2a Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Borgida 1995	25	13.5 (4.7)	25	22.6 (10.7)		100%	-9.1[-13.68,-4.52]
Total ***	**25**		**25**			**100%**	**-9.1[-13.68,-4.52]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.89(P<0.0001)							

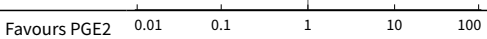
Analysis 18.2. Comparison 18 Comparison: PGE2 versus PGF2, Outcome 2 Abortion within 24 hours.

Study or subgroup	PGE2 n/N	PGF2a n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Borgida 1995	24/25	17/25		100%	11.29[1.29,98.89]
Total (95% CI)	**25**	**25**		**100%**	**11.29[1.29,98.89]**
Total events: 24 (PGE2), 17 (PGF2a)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.19(P=0.03)					

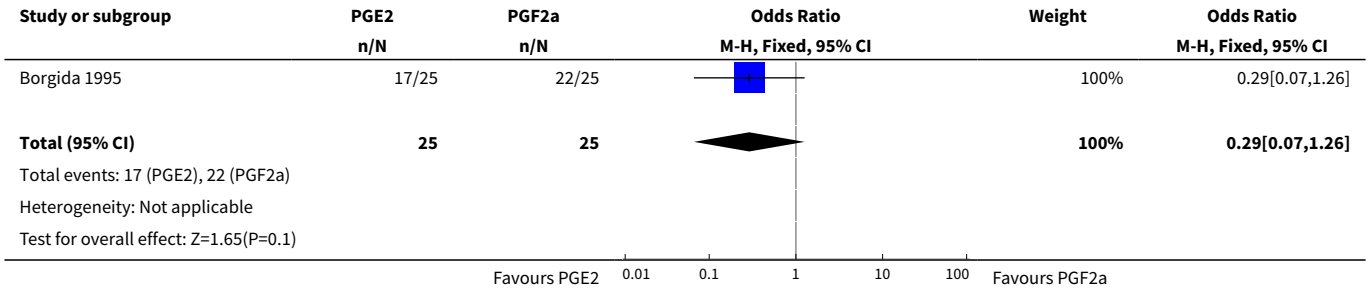


Analysis 18.3. Comparison 18 Comparison: PGE2 versus PGF2, Outcome 3 Pain.

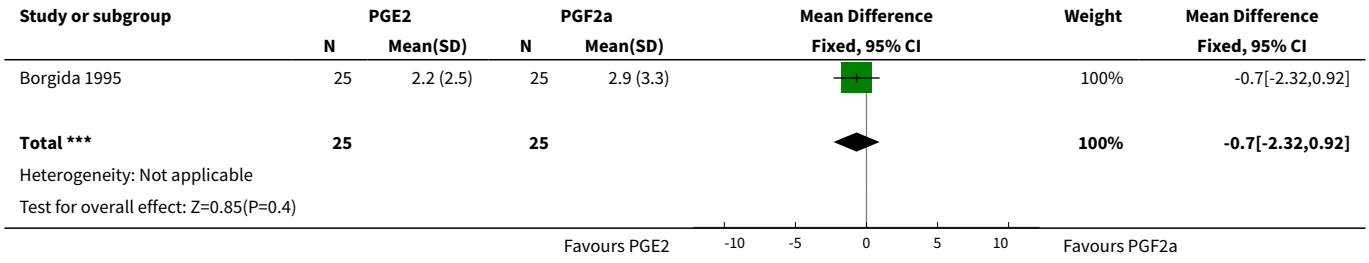
Study or subgroup	PGE2 n/N	PGF2a n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Borgida 1995	21/25	25/25		100%	0.09[0,1.84]
Total (95% CI)	**25**	**25**		**100%**	**0.09[0,1.84]**
Total events: 21 (PGE2), 25 (PGF2a)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.56(P=0.12)					



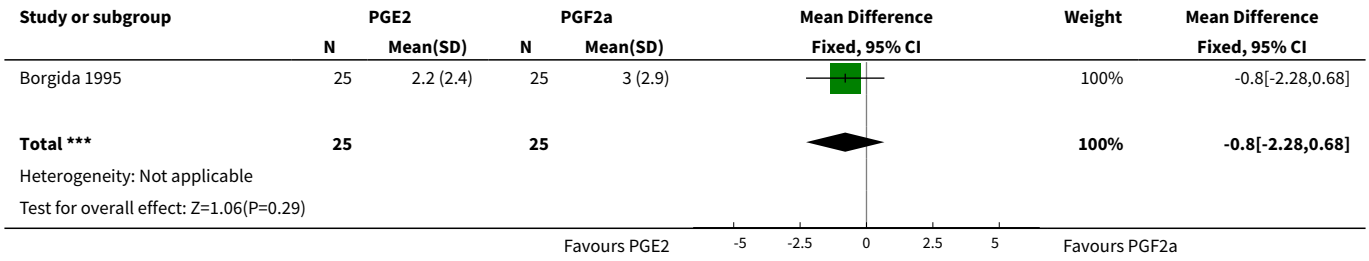
Analysis 18.4. Comparison 18 Comparison: PGE2 versus PGF2, Outcome 4 Nausea.



Analysis 18.5. Comparison 18 Comparison: PGE2 versus PGF2, Outcome 5 Vomiting.



Analysis 18.6. Comparison 18 Comparison: PGE2 versus PGF2, Outcome 6 Diarrhoea.

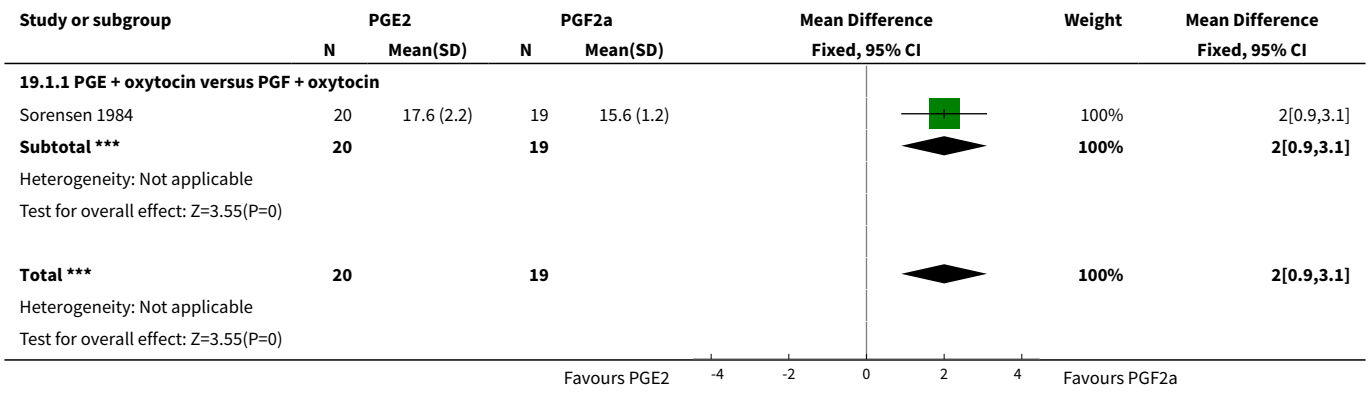


Comparison 19. Comparison: PGE2 versus PGF2+oxytocin

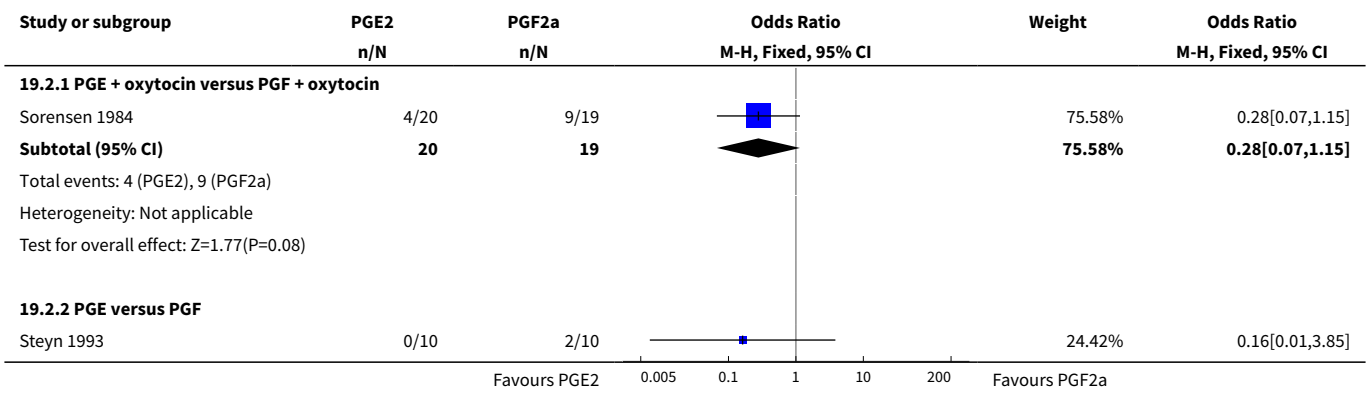
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	1	39	Mean Difference (IV, Fixed, 95% CI)	2.00 [0.90, 3.10]
1.1 PGE + oxytocin versus PGF + oxytocin	1	39	Mean Difference (IV, Fixed, 95% CI)	2.00 [0.90, 3.10]
2 Surgical evacuation	2	59	Odds Ratio (M-H, Fixed, 95% CI)	0.25 [0.07, 0.90]

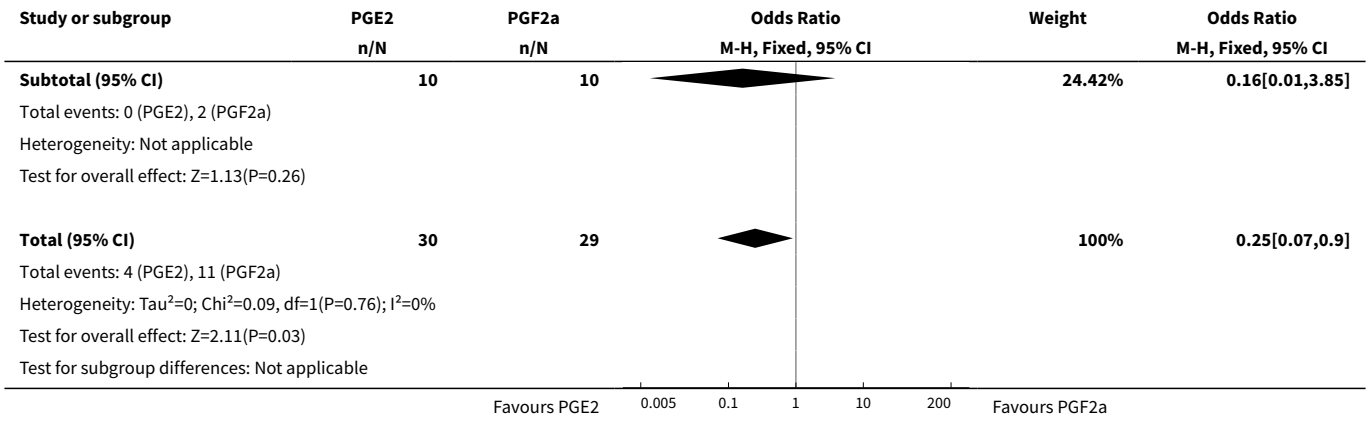
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 PGE + oxytocin versus PGF + oxytocin	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.07, 1.15]
2.2 PGE versus PGF	1	20	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 3.85]
3 Pain	1	20	Odds Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.72]
3.1 PGE versus PGF	1	20	Odds Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.72]
4 Vomiting	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.17, 2.17]
4.1 PGE + oxytocin versus PGF + oxytocin	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.17, 2.17]
5 Diarrhoea	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.06]
5.1 PGE + oxytocin versus PGF + oxytocin	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.06]

Analysis 19.1. Comparison 19 Comparison: PGE2 versus PGF2+oxytocin, Outcome 1 Induction to abortion interval.

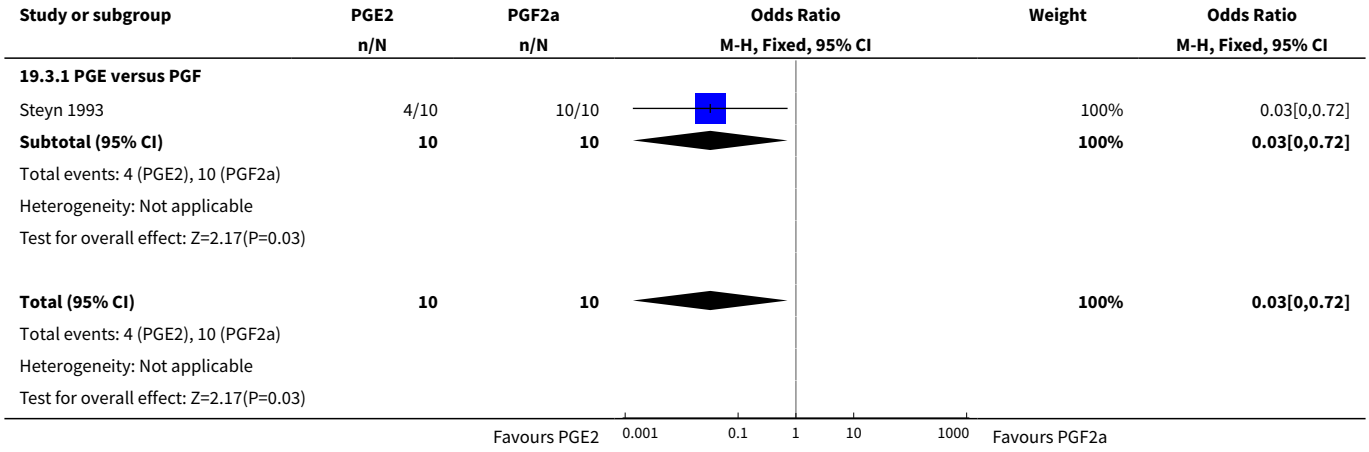


Analysis 19.2. Comparison 19 Comparison: PGE2 versus PGF2+oxytocin, Outcome 2 Surgical evacuation.

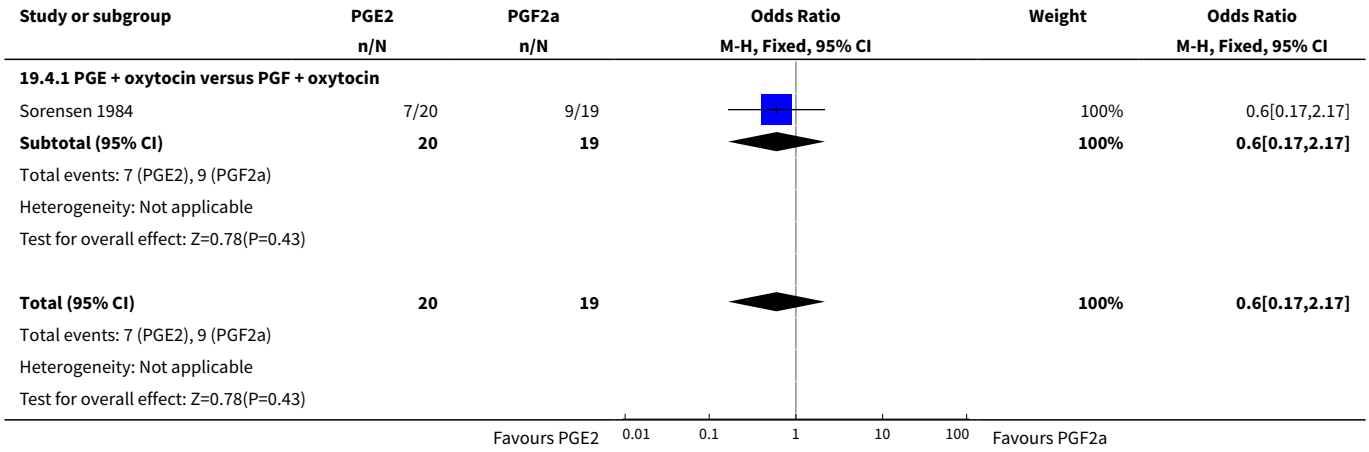




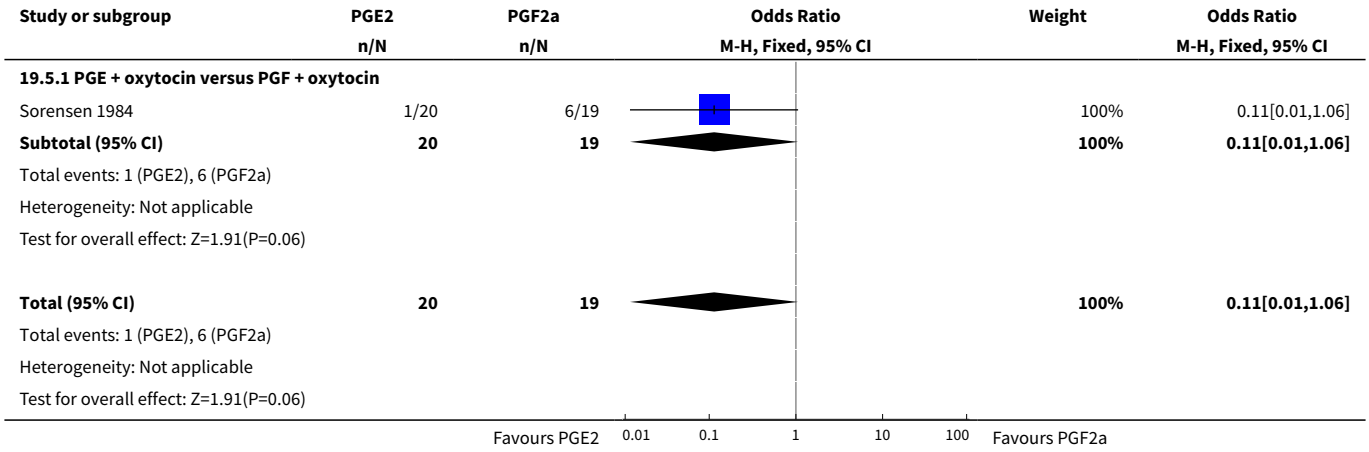
Analysis 19.3. Comparison 19 Comparison: PGE2 versus PGF2+oxytocin, Outcome 3 Pain.



Analysis 19.4. Comparison 19 Comparison: PGE2 versus PGF2+oxytocin, Outcome 4 Vomiting.



Analysis 19.5. Comparison 19 Comparison: PGE2 versus PGF2+oxytocin, Outcome 5 Diarrhoea.



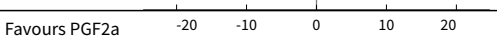
Comparison 20. Comparison: PGF2 versus hypertonic saline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	1	25	Mean Difference (IV, Fixed, 95% CI)	-5.30 [-6.67, -3.93]
1.1 20% NaCL versus single dose of 40 mg PGF	1	25	Mean Difference (IV, Fixed, 95% CI)	-5.30 [-6.67, -3.93]
2 Abortion within 24 hours	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 20% NaCL versus single dose of 50 mg PGF	1	67	Odds Ratio (M-H, Fixed, 95% CI)	1.52 [0.58, 3.98]
2.2 20% NaCl versus multiple doses of 25mg PGF	2	1579	Odds Ratio (M-H, Fixed, 95% CI)	6.14 [4.91, 7.68]
2.3 20% NaCL versus single dose of 40 mg PGF	1	32	Odds Ratio (M-H, Fixed, 95% CI)	15.78 [0.79, 314.27]
3 Blood loss >100 ml	3	165	Odds Ratio (M-H, Fixed, 95% CI)	2.50 [0.79, 7.91]
3.1 20% NaCL versus single dose of 50 mg PGF	1	67	Odds Ratio (M-H, Fixed, 95% CI)	8.30 [0.96, 71.72]
3.2 20% NaCL versus multuple doses of 25 mg PGF	1	66	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.23]
3.3 20% NaCL versus single dose of 40 mg PGF	1	32	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [0.23, 11.26]
4 Blood loss >500 ml	1	1513	Odds Ratio (M-H, Fixed, 95% CI)	3.05 [1.56, 5.97]

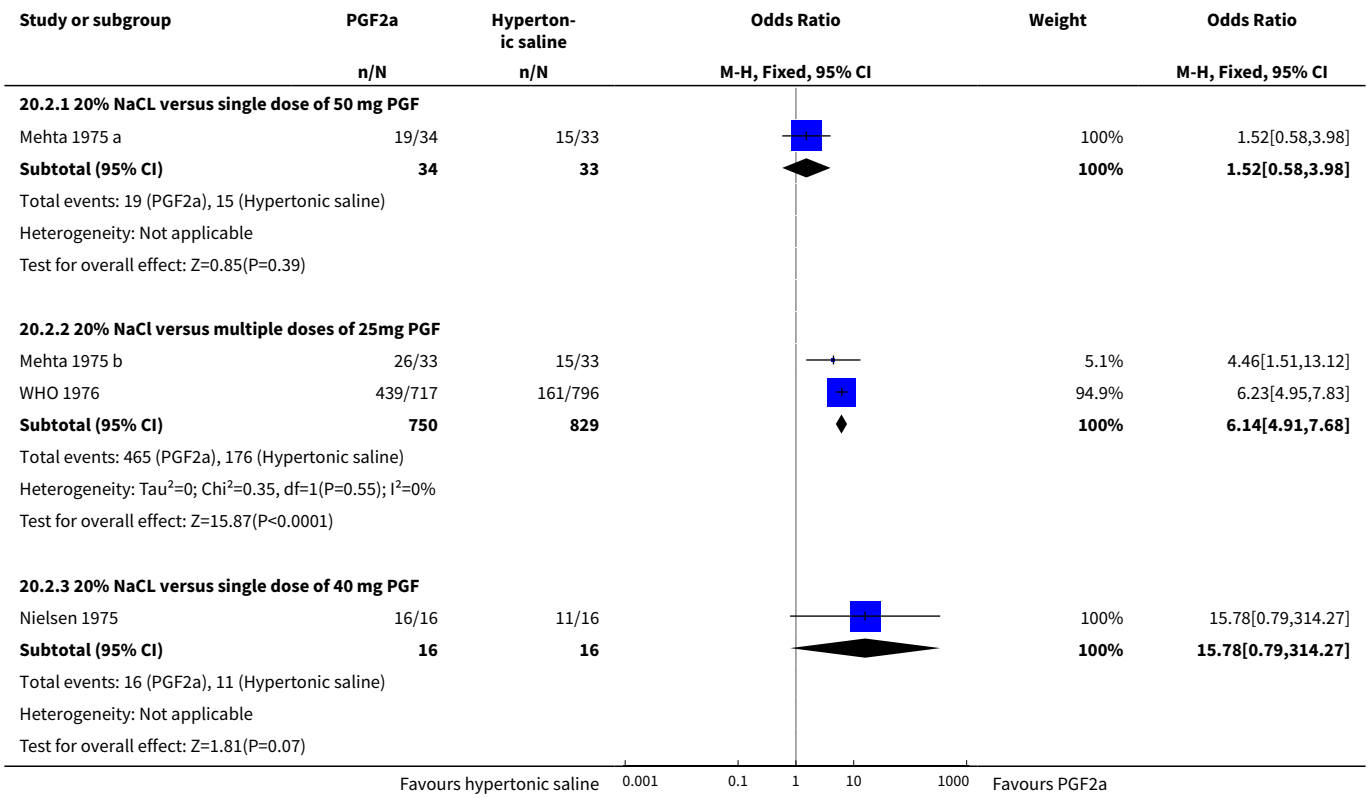
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 20% NaCL versus multiple doses of 25 mg PGF	1	1513	Odds Ratio (M-H, Fixed, 95% CI)	3.05 [1.56, 5.97]
5 Nausea	1	1513	Odds Ratio (M-H, Fixed, 95% CI)	3.01 [1.17, 7.72]
5.1 20% NaCL versus multiple doses of 25 mg PGF	1	1513	Odds Ratio (M-H, Fixed, 95% CI)	3.01 [1.17, 7.72]
6 Vomiting	3	1646	Odds Ratio (M-H, Fixed, 95% CI)	5.16 [4.12, 6.46]
6.1 20% NaCL versus single dose of 50 mg PGF	1	67	Odds Ratio (M-H, Fixed, 95% CI)	22.4 [2.73, 183.71]
6.2 20% NaCL versus multiple doses of 25 mg PGF	2	1579	Odds Ratio (M-H, Fixed, 95% CI)	5.01 [3.99, 6.28]
7 Diarrhoea	3	1646	Odds Ratio (M-H, Fixed, 95% CI)	10.83 [6.17, 19.02]
7.1 20% NaCL versus single dose of 50 mg PGF	1	67	Odds Ratio (M-H, Fixed, 95% CI)	2.07 [0.35, 12.13]
7.2 20% NaCL versus multiple doses of 25 mg PGF	2	1579	Odds Ratio (M-H, Fixed, 95% CI)	12.47 [6.81, 22.82]
8 Surgical evacuation	3	1646	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [1.30, 1.96]
8.1 20% NaCL versus single dose of 50 mg PGF	1	67	Odds Ratio (M-H, Fixed, 95% CI)	7.89 [2.01, 30.95]
8.2 20% NaCL versus multiple doses of 25 mg PGF	2	1579	Odds Ratio (M-H, Fixed, 95% CI)	1.52 [1.24, 1.87]

Analysis 20.1. Comparison 20 Comparison: PGF2 versus hypertonic saline, Outcome 1 Induction to abortion interval.

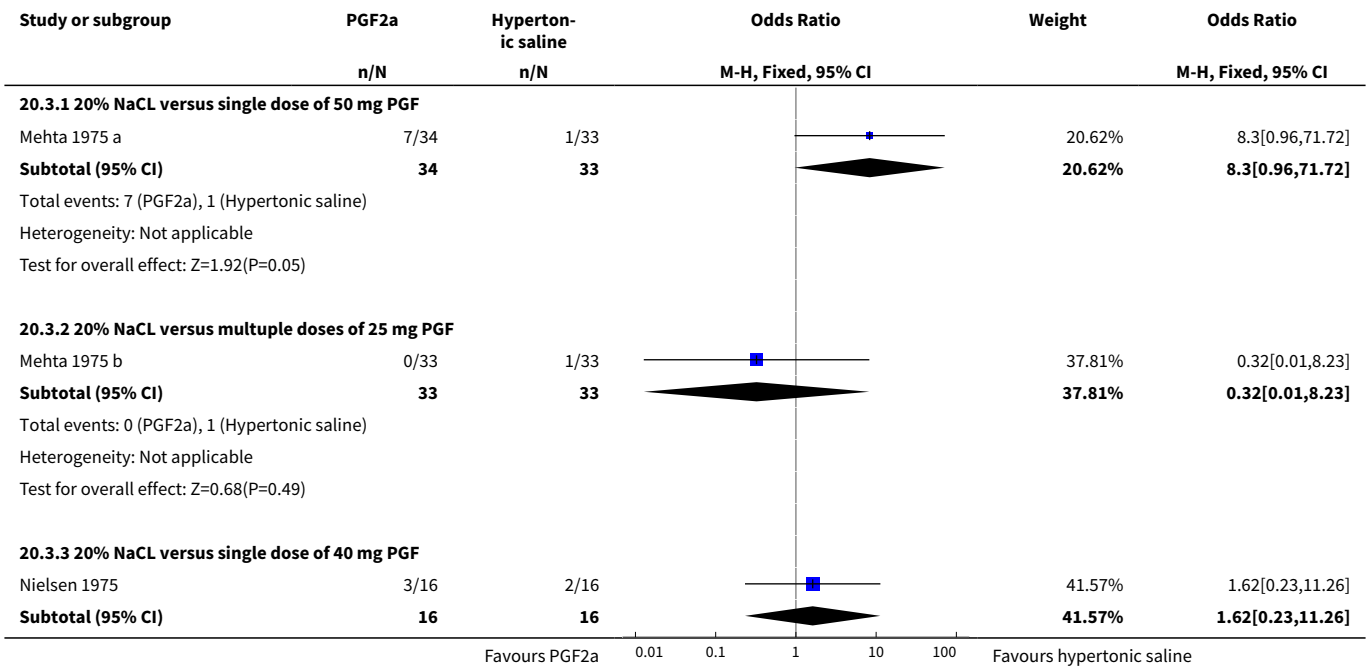
Study or subgroup	PGF2a N	PGF2a Mean(SD)	Hypertonic saline N	Hypertonic saline Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
20.1.1 20% NaCL versus single dose of 40 mg PGF							
Faktor 1988	9	13.1 (1.3)	16	18.4 (2.2)		100%	-5.3[-6.67,-3.93]
Subtotal ***	**9**		**16**			**100%**	**-5.3[-6.67,-3.93]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.57(P<0.0001)							
Total ***	**9**		**16**			**100%**	**-5.3[-6.67,-3.93]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.57(P<0.0001)							

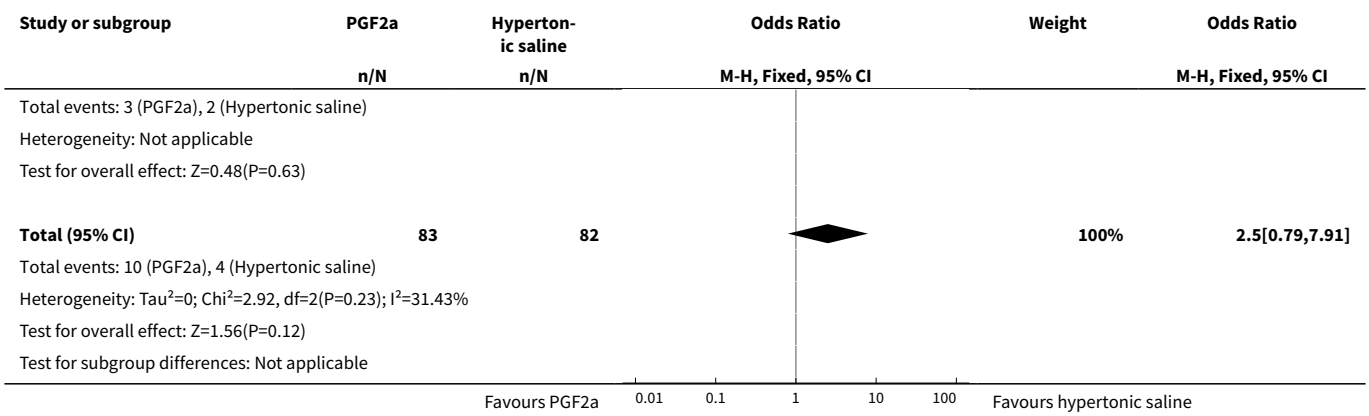


Analysis 20.2. Comparison 20 Comparison: PGF2 versus hypertonic saline, Outcome 2 Abortion within 24 hours.

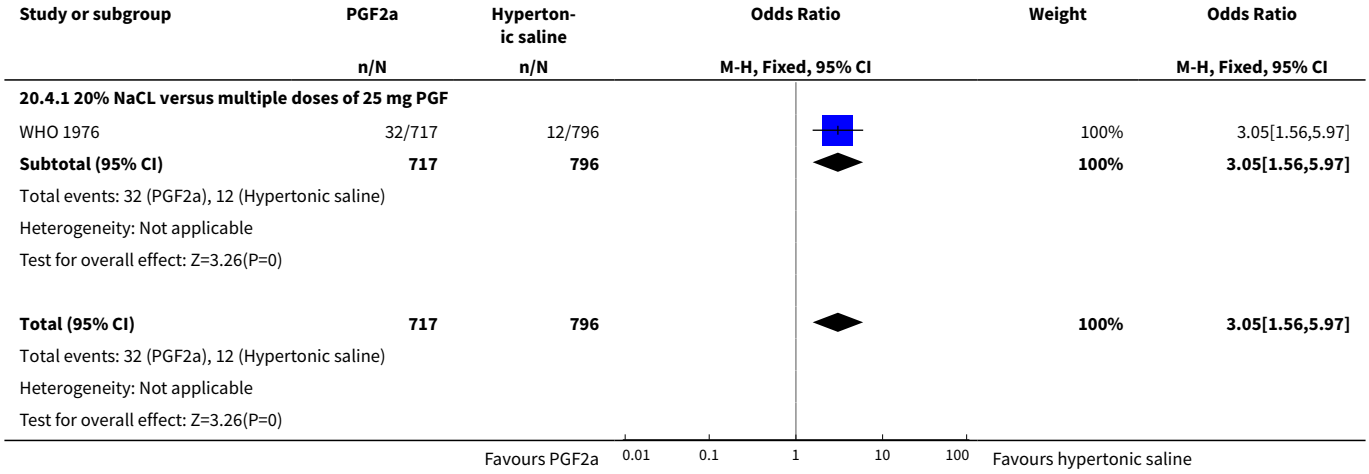


Analysis 20.3. Comparison 20 Comparison: PGF2 versus hypertonic saline, Outcome 3 Blood loss >100 ml.

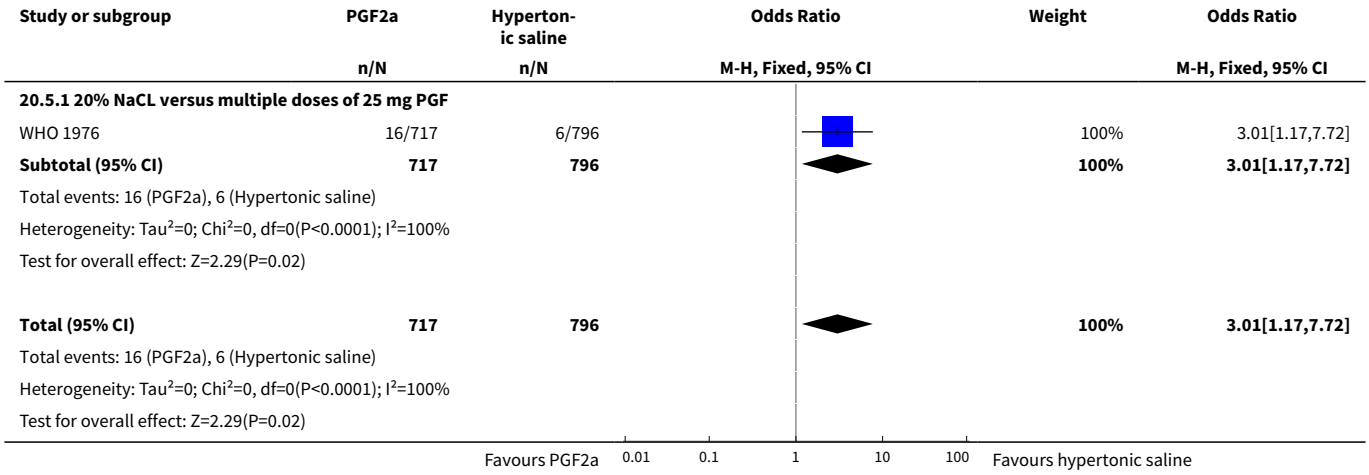




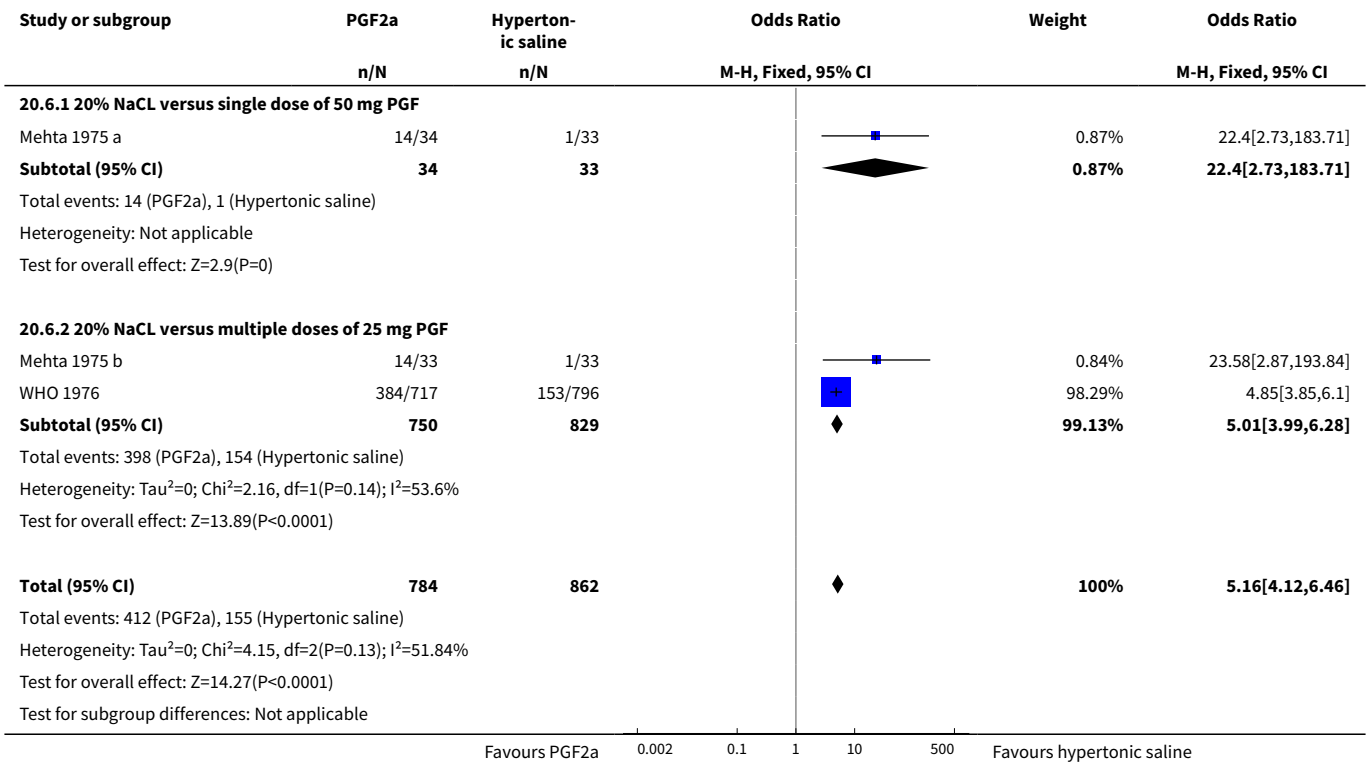
Analysis 20.4. Comparison 20 Comparison: PGF2 versus hypertonic saline, Outcome 4 Blood loss >500 ml.



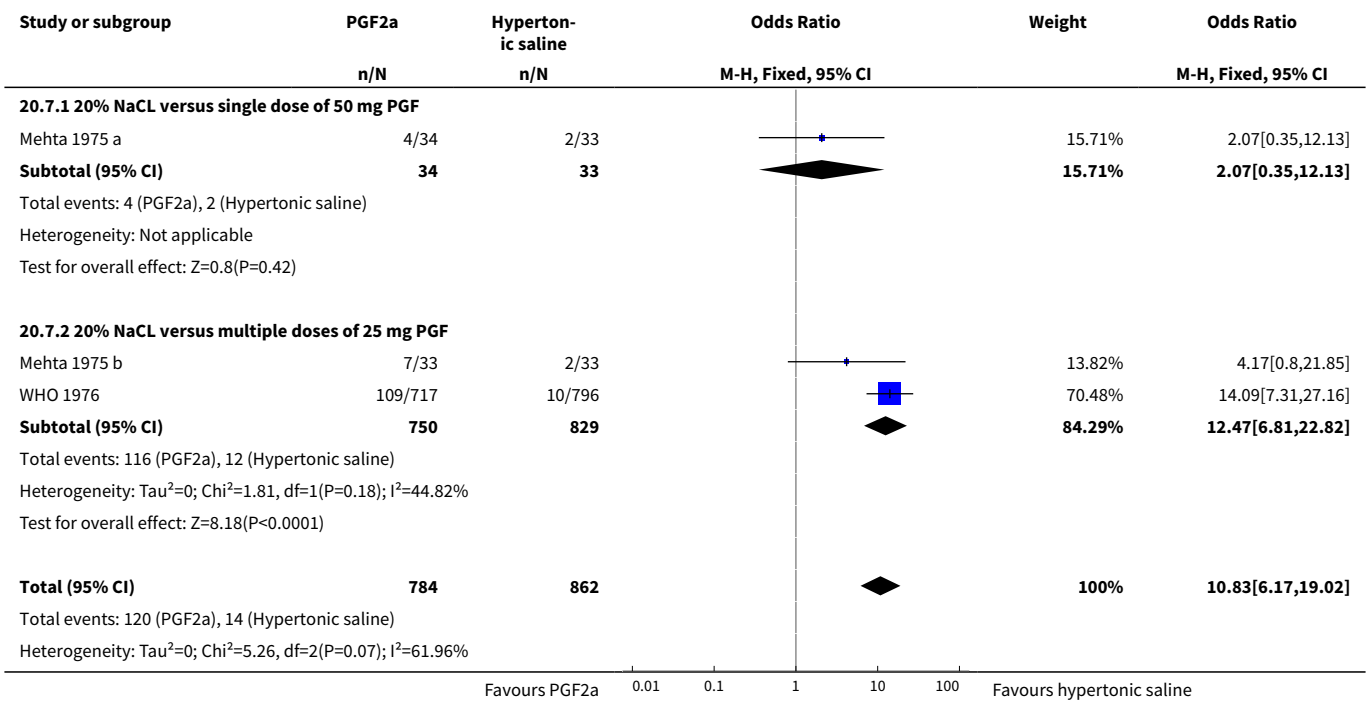
Analysis 20.5. Comparison 20 Comparison: PGF2 versus hypertonic saline, Outcome 5 Nausea.

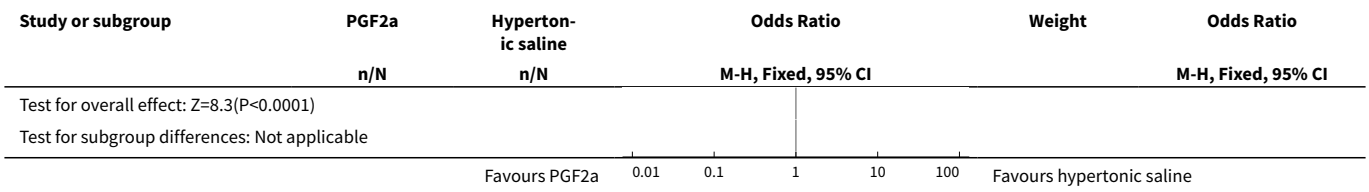


Analysis 20.6. Comparison 20 Comparison: PGF2 versus hypertonic saline, Outcome 6 Vomiting.

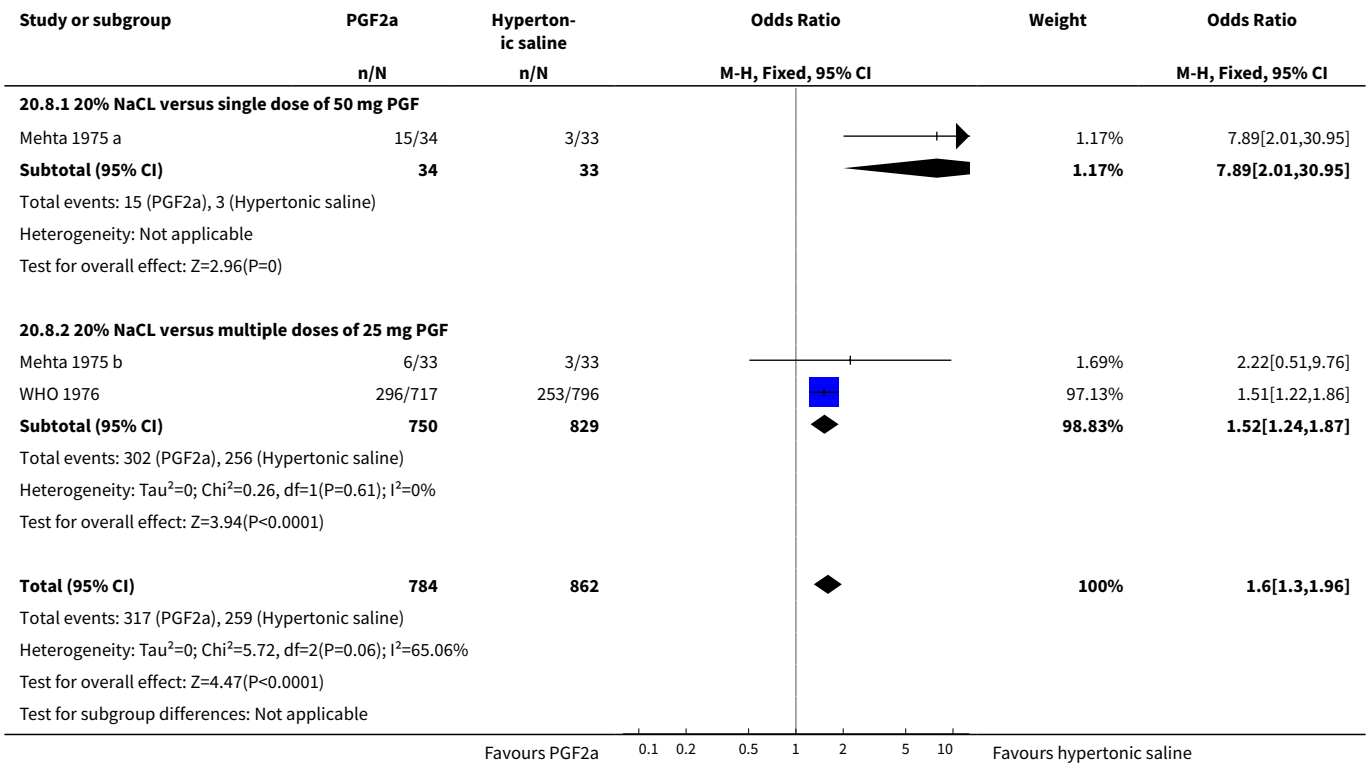


Analysis 20.7. Comparison 20 Comparison: PGF2 versus hypertonic saline, Outcome 7 Diarrhoea.





Analysis 20.8. Comparison 20 Comparison: PGF2 versus hypertonic saline, Outcome 8 Surgical evacuation.



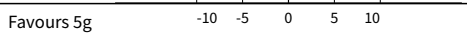
Comparison 21. Comparison: combined regimen PGF2+hypertonic saline

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Induction to abortion interval	4	770	Mean Difference (IV, Fixed, 95% CI)	-1.55 [-3.53, 0.44]
1.1 100 ml 5% NaCl versus 100 ml 10% NaCl combined with PGF	2	230	Mean Difference (IV, Fixed, 95% CI)	2.21 [-1.59, 6.00]
1.2 25 ml 20% NaCl versus 100 ml 10% NaCl combined with PGF	2	540	Mean Difference (IV, Fixed, 95% CI)	-2.96 [-5.29, -0.64]
2 Abortion within 24 hours	4	770	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.90, 1.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 100 ml 5% NaCl versus 100 ml 10% NaCl combined with PGF	2	230	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.38, 1.26]
2.2 25 ml 20% NaCl versus 100 ml 10% NaCl combined with PGF	2	540	Odds Ratio (M-H, Fixed, 95% CI)	2.30 [1.38, 3.86]
3 Blood loss (>500 ml)	4	770	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.66, 1.95]
3.1 100 ml 5% NaCl versus 100 ml 10% NaCl combined with PGF	2	230	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.23, 1.78]
3.2 25 ml 20% NaCl versus 100 ml 10% NaCl combined with PGF	2	540	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.74, 2.80]
4 Surgical evacuation	4	770	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.66, 1.95]
4.1 100 ml 5% NaCl versus 100 ml 10% NaCl combined with PGF	2	230	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.23, 1.78]
4.2 25 ml 20% NaCl versus 100 ml 10% NaCl combined with PGF	2	540	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.74, 2.80]
5 Nausea	4	770	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.35, 0.94]
5.1 100 ml 5% NaCl versus 100 ml 10% NaCl combined with PGF	2	230	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.52, 2.19]
5.2 25 ml 20% NaCl versus 100 ml 10% NaCl combined with PGF	2	540	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.17, 0.62]
6 Vomiting	4	770	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.44, 1.72]
6.1 100 ml 5% NaCl versus 100 ml 10% NaCl combined with PGF	2	230	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.33, 3.06]
6.2 25 ml 20% NaCl versus 100 ml 10% NaCl combined with PGF	2	540	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.34, 1.87]
7 Diarrhoea	4	770	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.24, 4.83]
7.1 100 ml 5% NaCl versus 100 ml 10% NaCl combined with PGF	2	230	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.02, 13.13]
7.2 25 ml 20% NaCl versus 100 ml 10% NaCl combined with PGF	2	540	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.23, 8.33]

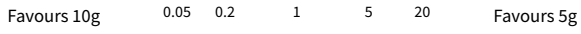
Analysis 21.1. Comparison 21 Comparison: combined regimen PGF2+hypertonic saline, Outcome 1 Induction to abortion interval.

Study or subgroup	5g hyper-tonic saline N	5g hyper-tonic saline Mean(SD)	10g hyper-tonic saline N	10g hyper-tonic saline Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
21.1.1 100 ml 5% NaCl versus 100 ml 10% NaCl combined with PGF							
Muzsnai 1979 a	50	20.7 (15.7)	50	19.6 (13.3)		12.15%	1.07[-4.62,6.76]
Muzsnai 1979 b	50	20.7 (15.7)	80	17.6 (12)		15.25%	3.11[-1.97,8.19]
Subtotal ***	**100**		**130**			**27.4%**	**2.21[-1.59,6]**
Heterogeneity: Tau^2=0; Chi^2=0.27, df=1(P=0.6); I^2=0%							
Test for overall effect: Z=1.14(P=0.25)							
21.1.2 25 ml 20% NaCl versus 100 ml 10% NaCl combined with PGF							
Muzsnai 1979 c	205	15.3 (9.1)	50	19.6 (13.3)		26.14%	-4.27[-8.15,-0.39]
Muzsnai 1979 d	205	15.3 (9.1)	80	17.6 (12)		46.46%	-2.23[-5.14,0.68]
Subtotal ***	**410**		**130**			**72.6%**	**-2.96[-5.29,-0.64]**
Heterogeneity: Tau^2=0; Chi^2=0.68, df=1(P=0.41); I^2=0%							
Test for overall effect: Z=2.49(P=0.01)							
Total ***	**510**		**260**			**100%**	**-1.55[-3.53,0.44]**
Heterogeneity: Tau^2=0; Chi^2=6.14, df=3(P=0.11); I^2=51.13%							
Test for overall effect: Z=1.53(P=0.13)							
Test for subgroup differences: Chi^2=5.19, df=1 (P=0.02), I^2=80.72%							

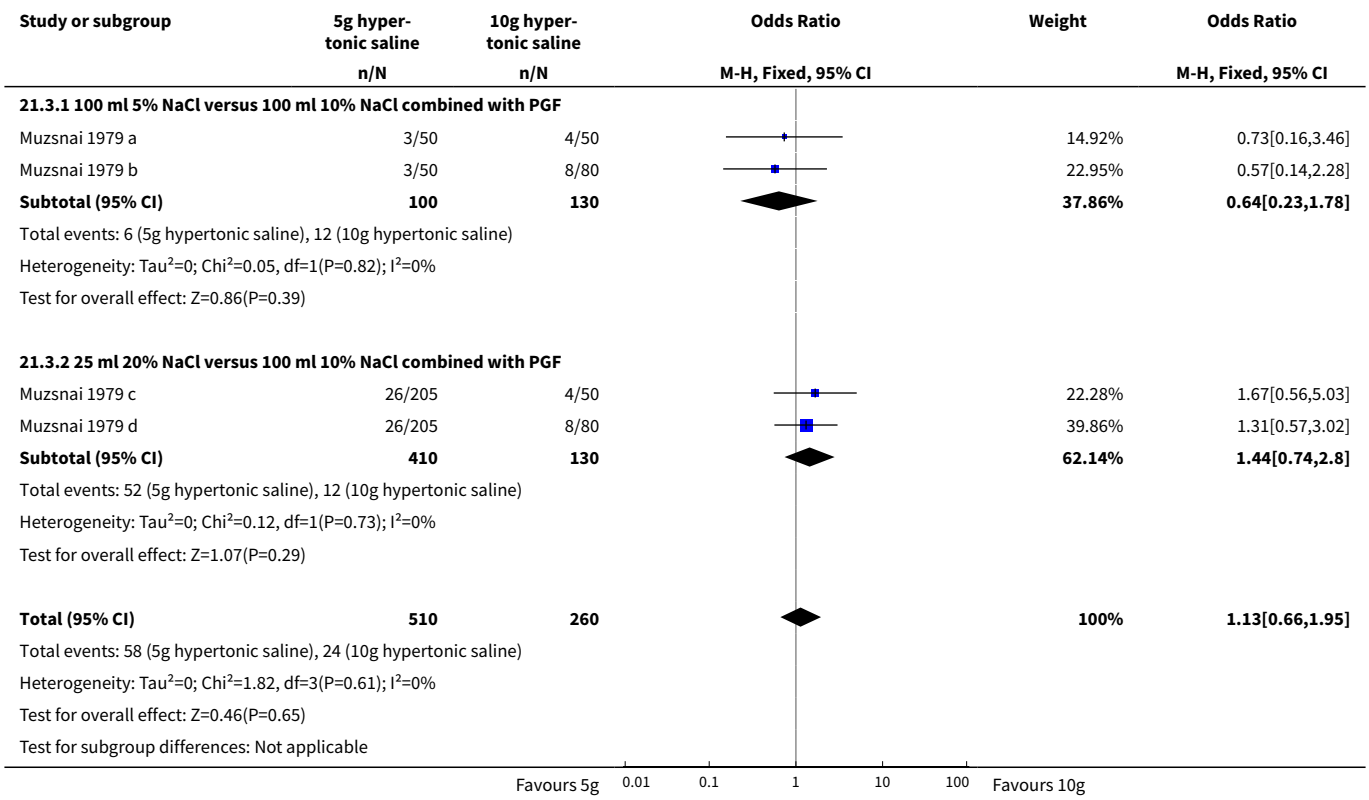


Analysis 21.2. Comparison 21 Comparison: combined regimen PGF2+hypertonic saline, Outcome 2 Abortion within 24 hours.

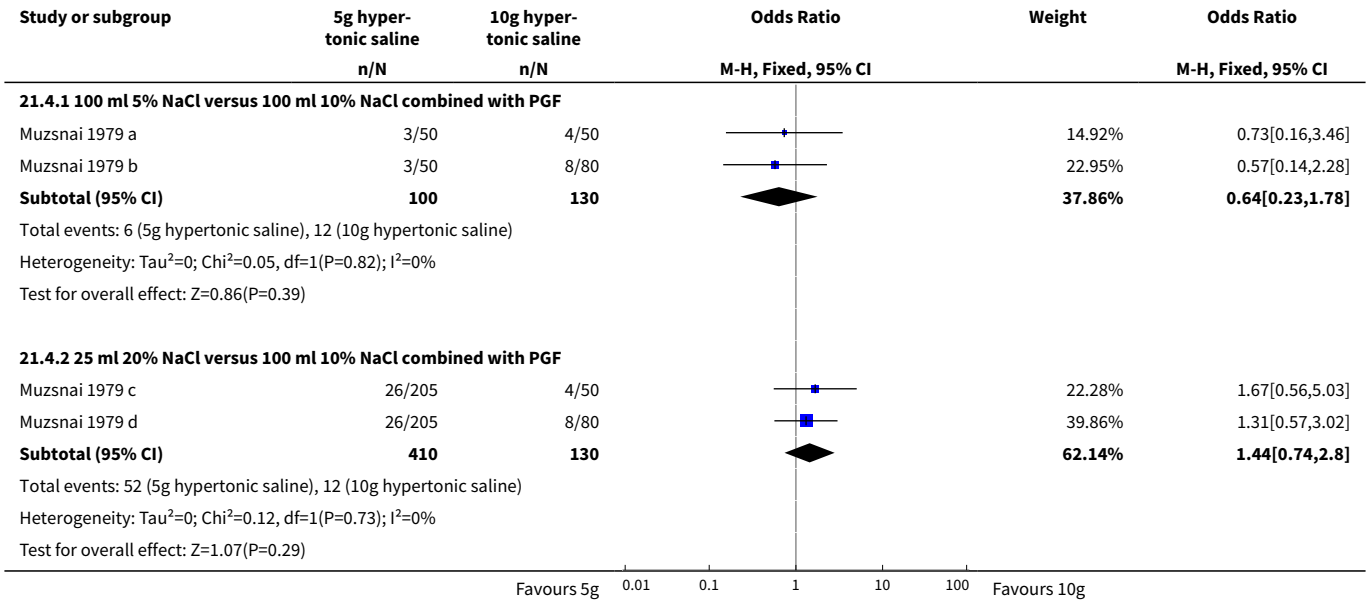
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
21.2.1 100 ml 5% NaCl versus 100 ml 10% NaCl combined with PGF					
Muzsnai 1979 a	35/50	36/50		25.24%	0.91[0.38,2.15]
Muzsnai 1979 b	35/50	65/80		35.06%	0.54[0.24,1.23]
Subtotal (95% CI)	**100**	**130**		**60.3%**	**0.69[0.38,1.26]**
Total events: 70 (Experimental), 101 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.73, df=1(P=0.39); I^2=0%					
Test for overall effect: Z=1.21(P=0.23)					
21.2.2 25 ml 20% NaCl versus 100 ml 10% NaCl combined with PGF					
Muzsnai 1979 c	182/205	36/50		15.18%	3.08[1.45,6.54]
Muzsnai 1979 d	182/205	65/80		24.52%	1.83[0.9,3.71]
Subtotal (95% CI)	**410**	**130**		**39.7%**	**2.3[1.38,3.86]**
Total events: 364 (Experimental), 101 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.98, df=1(P=0.32); I^2=0%					
Test for overall effect: Z=3.17(P=0)					
Total (95% CI)	**510**	**260**		**100%**	**1.33[0.9,1.97]**
Total events: 434 (Experimental), 202 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.88, df=3(P=0.01); I^2=72.42%					
Test for overall effect: Z=1.44(P=0.15)					
Test for subgroup differences: Not applicable					

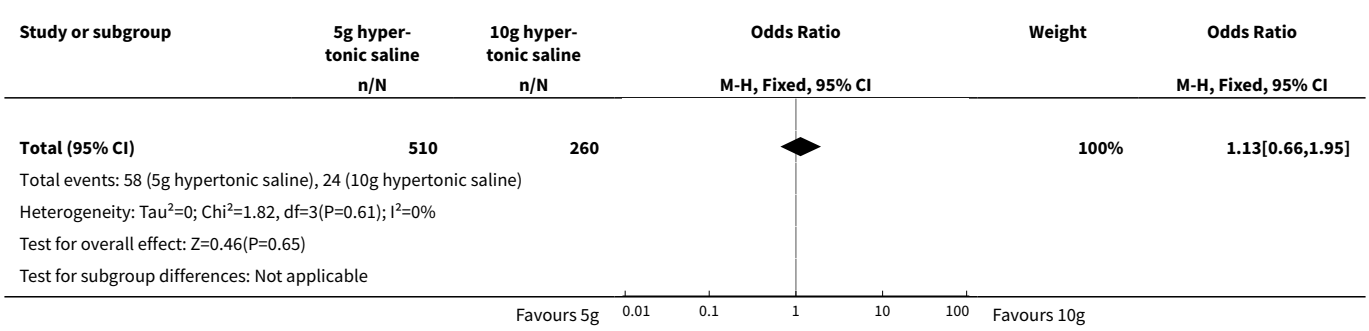


Analysis 21.3. Comparison 21 Comparison: combined regimen PGF2+hypertonic saline, Outcome 3 Blood loss (>500 ml).

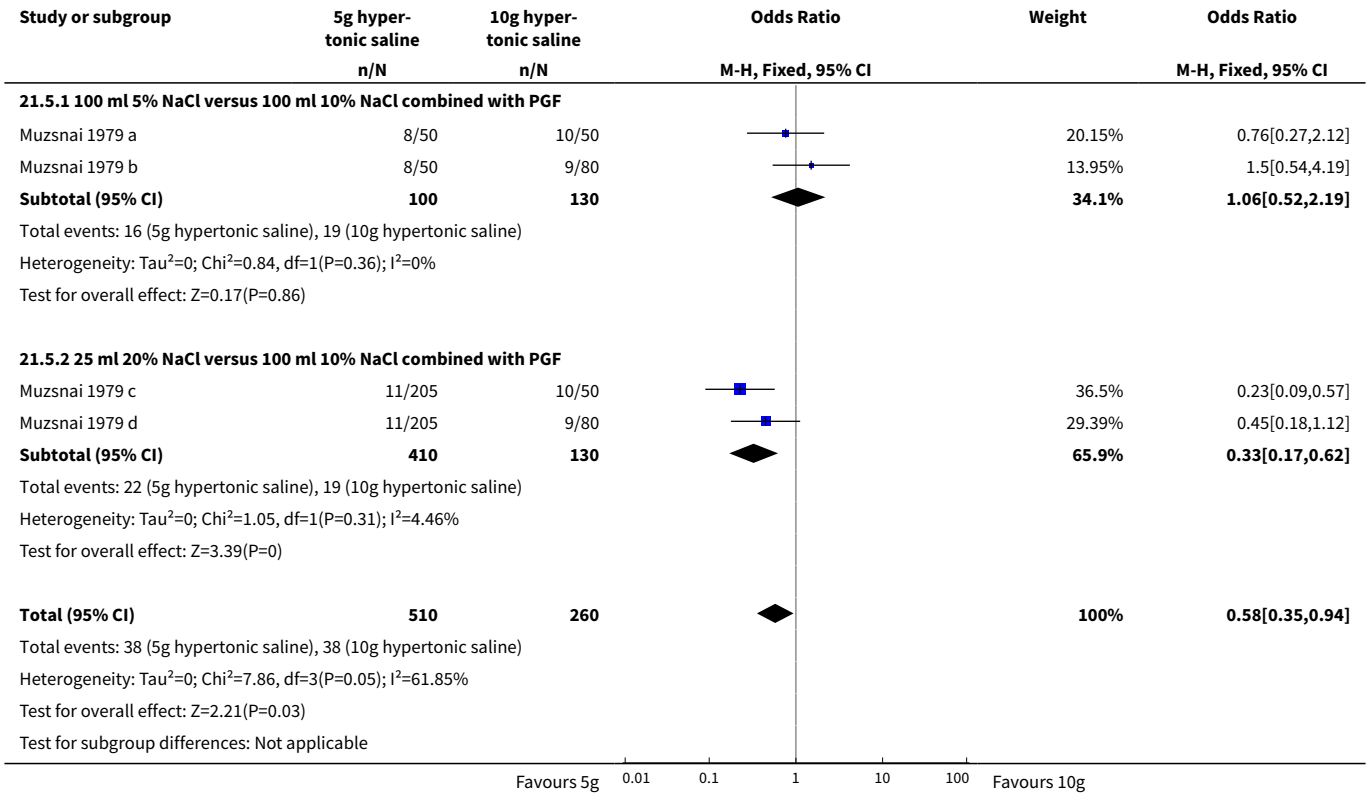


Analysis 21.4. Comparison 21 Comparison: combined regimen PGF2+hypertonic saline, Outcome 4 Surgical evacuation.

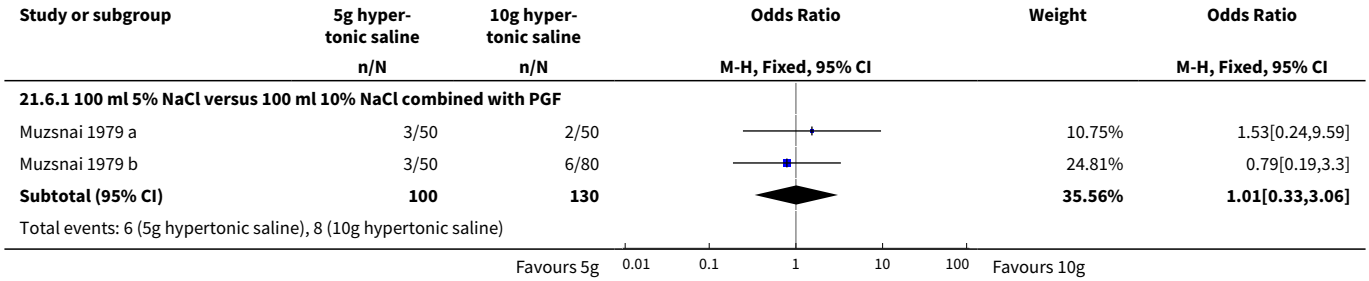


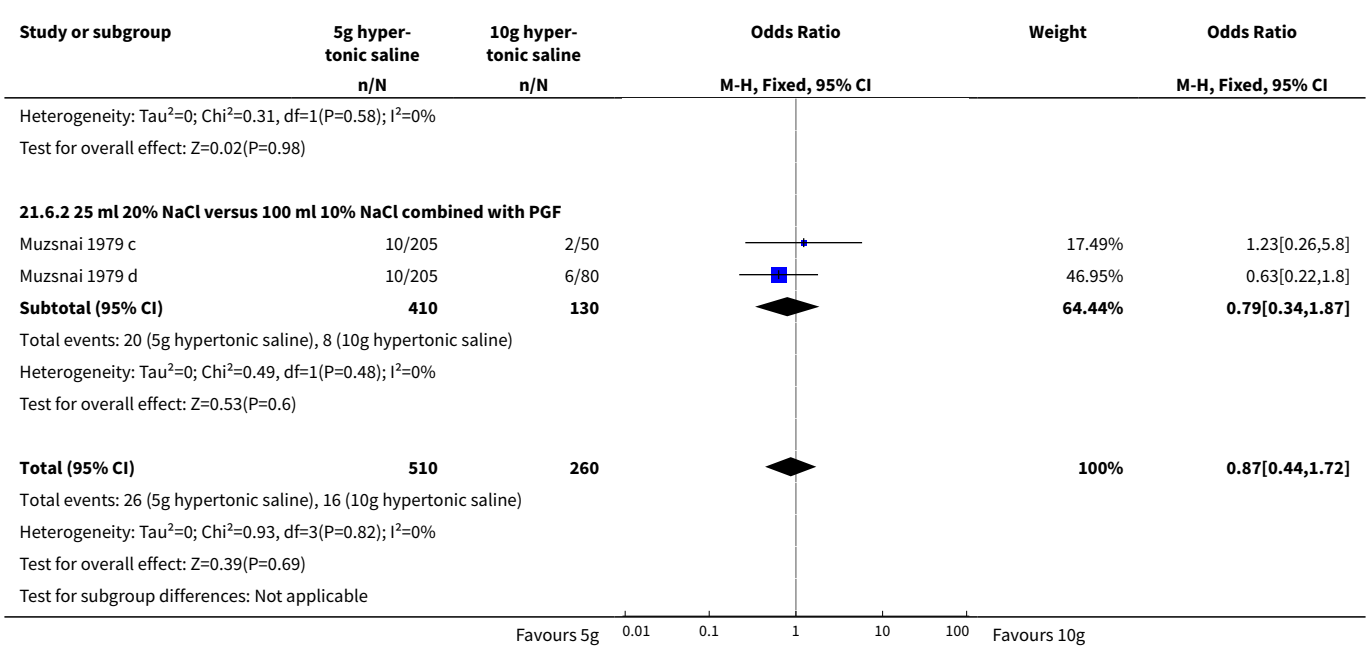


Analysis 21.5. Comparison 21 Comparison: combined regimen PGF2+hypertonic saline, Outcome 5 Nausea.

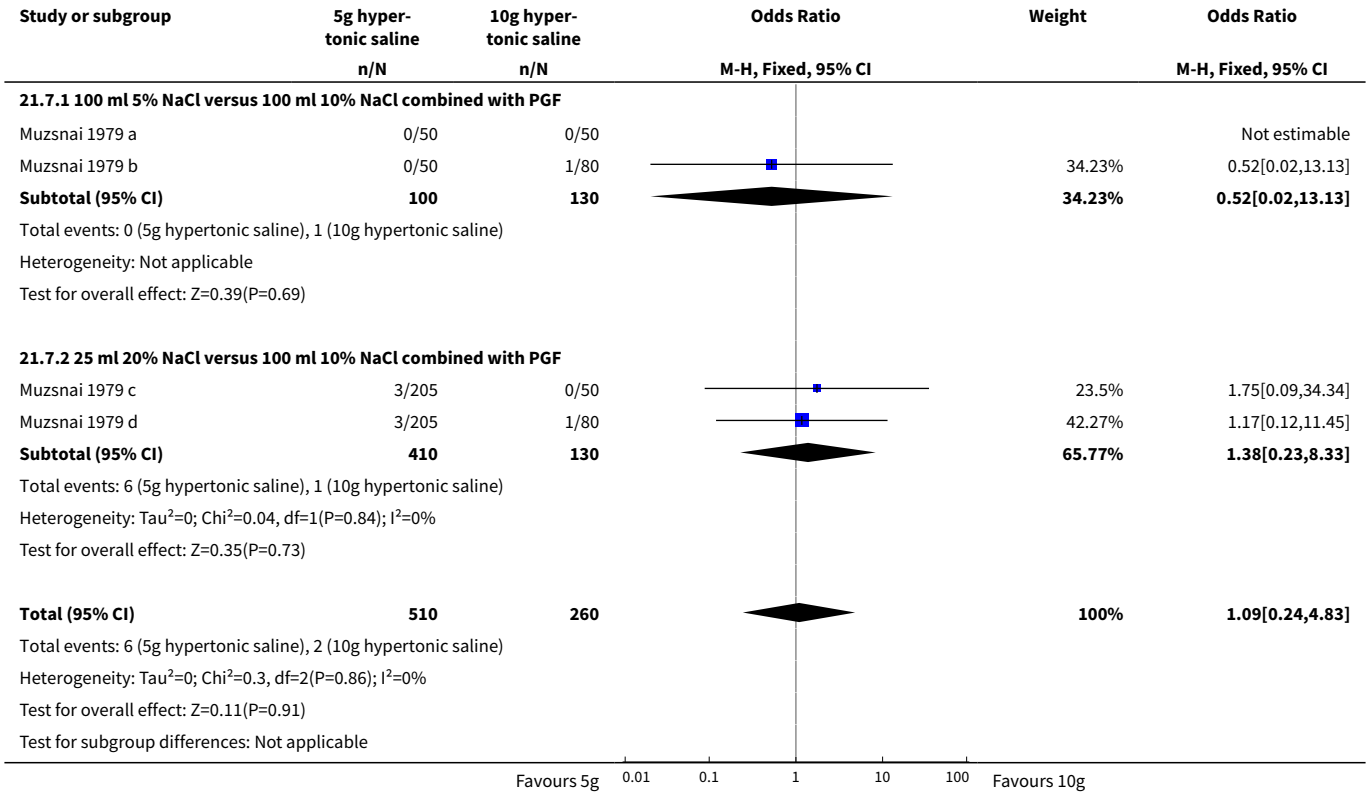


Analysis 21.6. Comparison 21 Comparison: combined regimen PGF2+hypertonic saline, Outcome 6 Vomiting.





Analysis 21.7. Comparison 21 Comparison: combined regimen PGF2+hypertonic saline, Outcome 7 Diarrhoea.

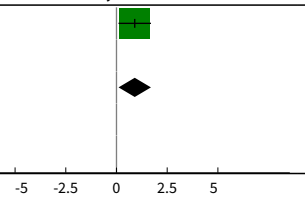


Comparison 22. Comparison: PGE1 versus PGF2+hypertonic saline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	1	58	Mean Difference (IV, Fixed, 95% CI)	0.90 [0.10, 1.70]
2 Abortion within 24h	1	58	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.04, 0.67]
3 Blood loss (>300ml)	1	58	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.79]
4 Surgical evacuation	1	58	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [0.54, 4.34]
5 Pain (pethidine)	1	58	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.10, 4.16]
6 Vomiting	1	58	Odds Ratio (M-H, Fixed, 95% CI)	3.11 [1.06, 9.08]
7 Diarrhoea	1	58	Odds Ratio (M-H, Fixed, 95% CI)	19.13 [3.80, 96.18]

Analysis 22.1. Comparison 22 Comparison: PGE1 versus PGF2+hypertonic saline, Outcome 1 Induction to abortion interval.

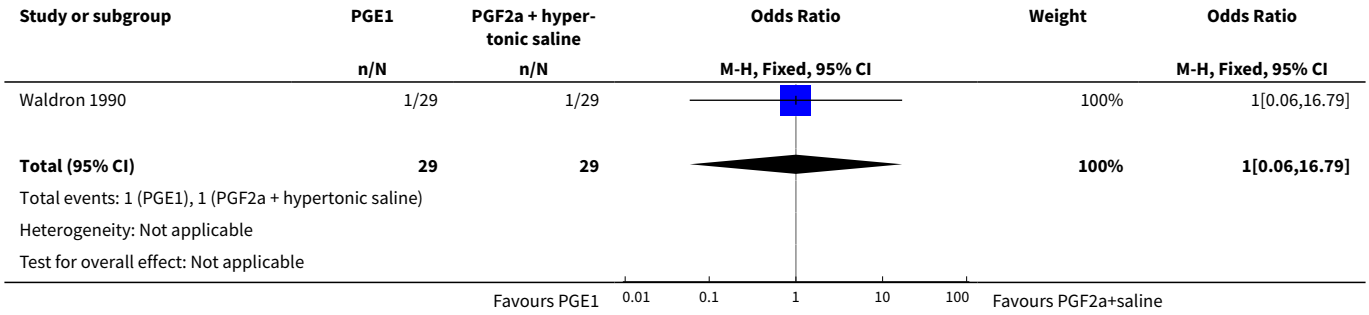
Study or subgroup	PGE1 N	PGE1 Mean(SD)	PGF2a + hypertonic saline N	PGF2a + hypertonic saline Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Waldron 1990	29	12.6 (1.9)	29	11.7 (1.1)		100%	0.9[0.1,1.7]
Total * **	**29**		**29**			**100%**	**0.9[0.1,1.7]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.21(P=0.03)							



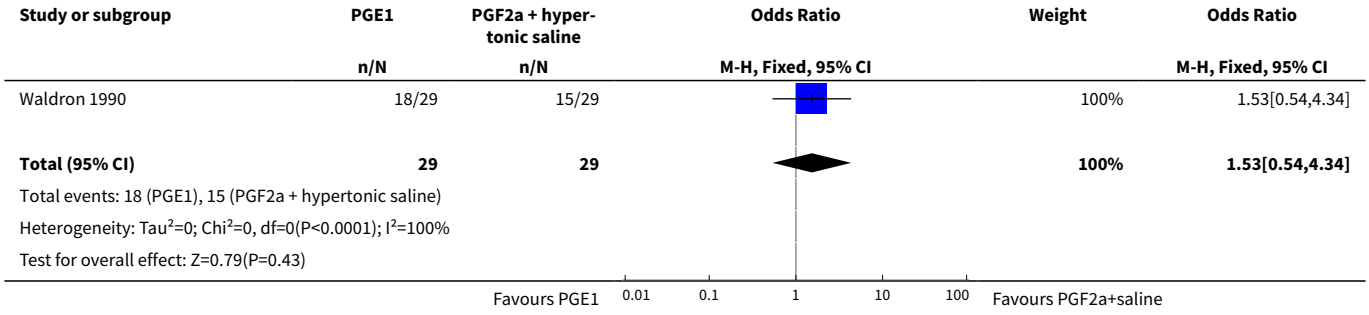
Analysis 22.2. Comparison 22 Comparison: PGE1 versus PGF2+hypertonic saline, Outcome 2 Abortion within 24h.

Study or subgroup	PGE1 n/N	PGF2a + hypertonic saline n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Waldron 1990	17/29	26/29		100%	0.16[0.04,0.67]
Total (95% CI)	**29**	**29**		**100%**	**0.16[0.04,0.67]**
Total events: 17 (PGE1), 26 (PGF2a + hypertonic saline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.53(P=0.01)					

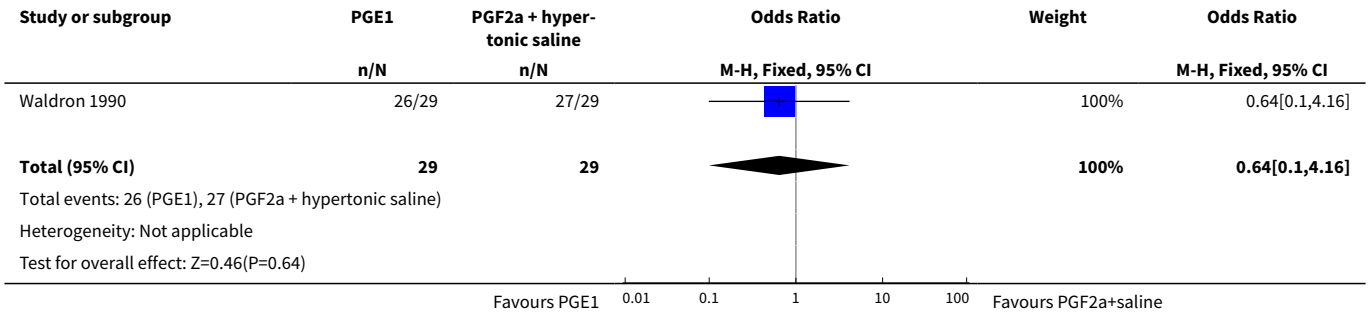
Analysis 22.3. Comparison 22 Comparison: PGE1 versus PGF2+hypertonic saline, Outcome 3 Blood loss (>300ml).



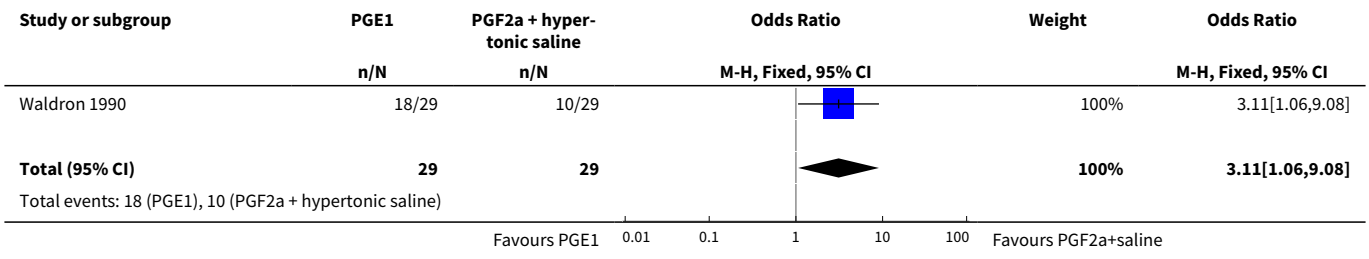
Analysis 22.4. Comparison 22 Comparison: PGE1 versus PGF2+hypertonic saline, Outcome 4 Surgical evacuation.

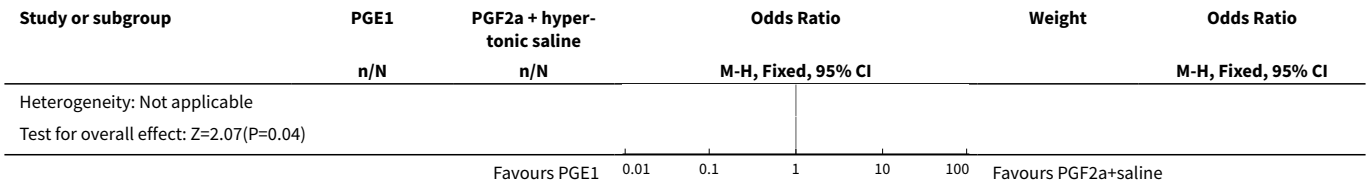


Analysis 22.5. Comparison 22 Comparison: PGE1 versus PGF2+hypertonic saline, Outcome 5 Pain (pethidine).

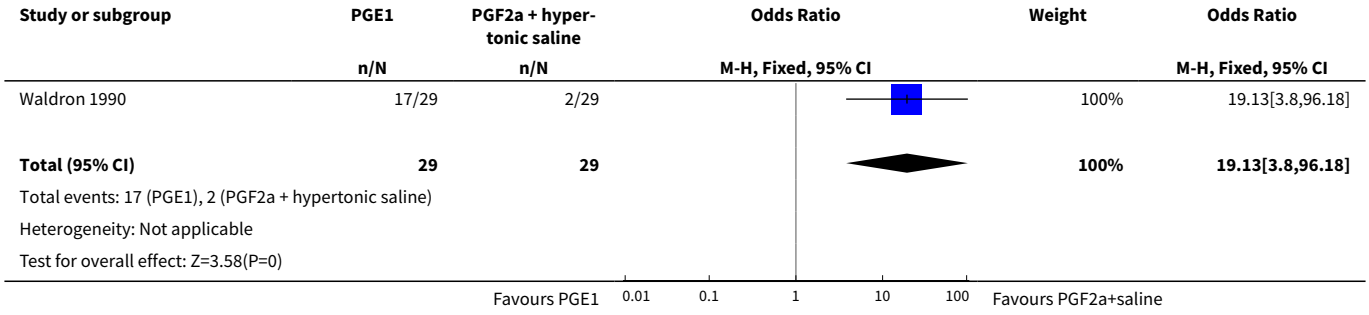


Analysis 22.6. Comparison 22 Comparison: PGE1 versus PGF2+hypertonic saline, Outcome 6 Vomiting.





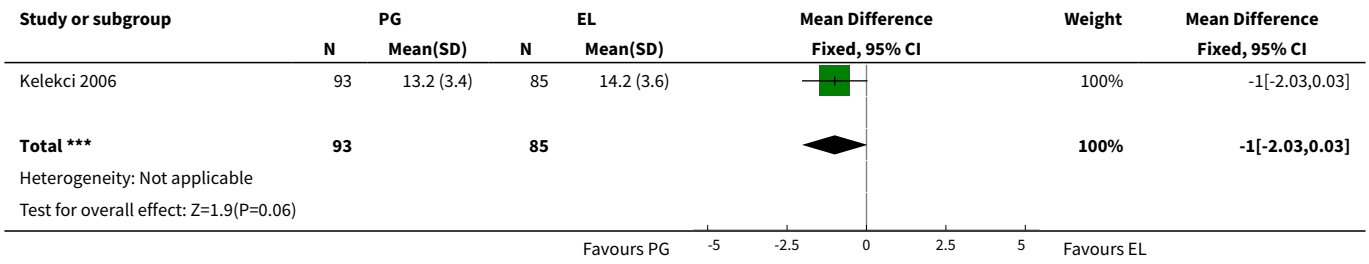
Analysis 22.7. Comparison 22 Comparison: PGE1 versus PGF2+hypertonic saline, Outcome 7 Diarrhoea.



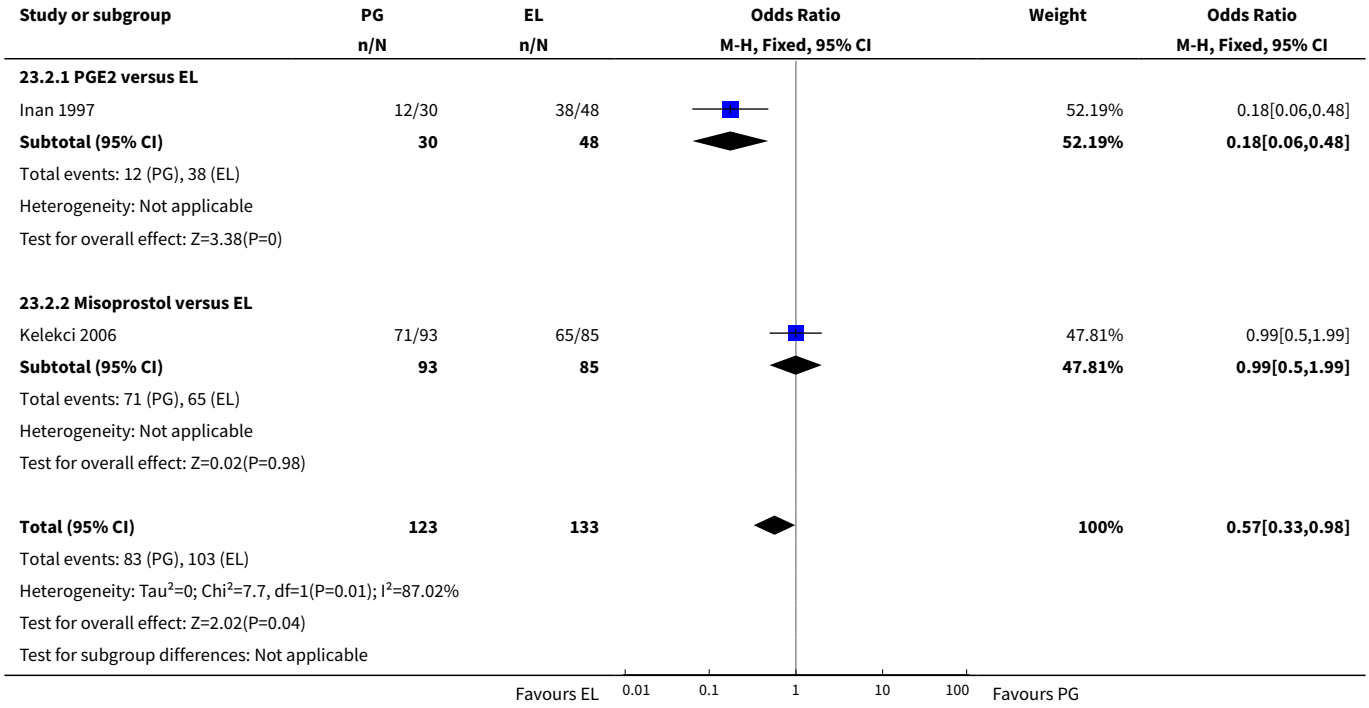
Comparison 23. Comparison: prostaglandin versus ethacridine lactate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	1	178	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.03, 0.03]
2 Abortion within 24h	2	256	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.33, 0.98]
2.1 PGE2 versus EL	1	78	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.06, 0.48]
2.2 Misoprostol versus EL	1	178	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.50, 1.99]
3 Blood loss	1	46	Odds Ratio (M-H, Fixed, 95% CI)	2.10 [0.18, 24.87]
4 Nausea	2	124	Odds Ratio (M-H, Fixed, 95% CI)	2.26 [0.79, 6.46]
5 Vomiting	1	46	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.37, 3.81]
6 Diarrhoea	1	46	Odds Ratio (M-H, Fixed, 95% CI)	5.47 [0.25, 120.37]

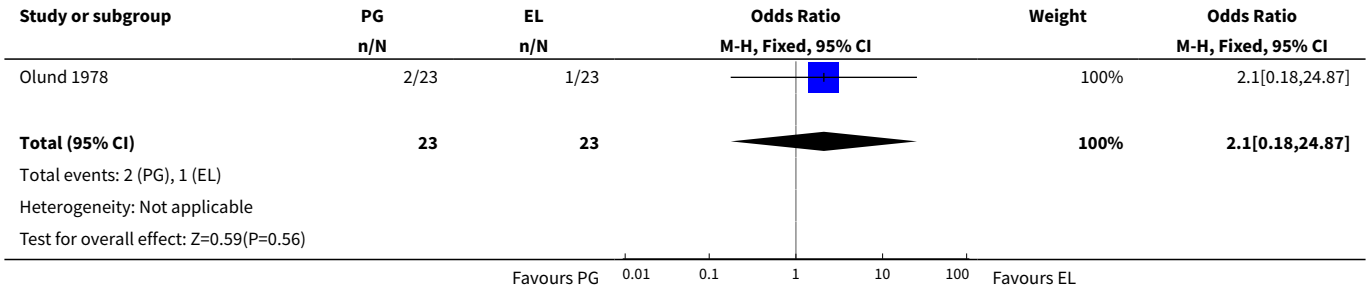
Analysis 23.1. Comparison 23 Comparison: prostaglandin versus ethacridine lactate, Outcome 1 Induction to abortion interval.



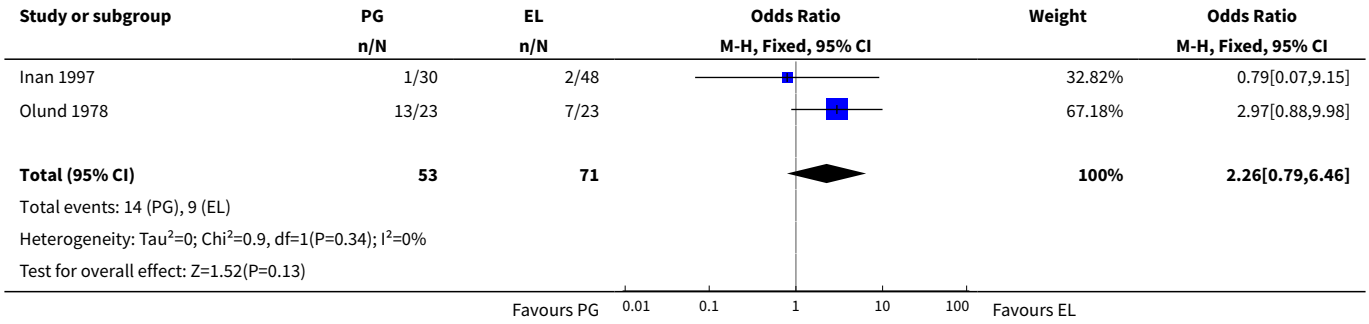
Analysis 23.2. Comparison 23 Comparison: prostaglandin versus ethacridine lactate, Outcome 2 Abortion within 24h.



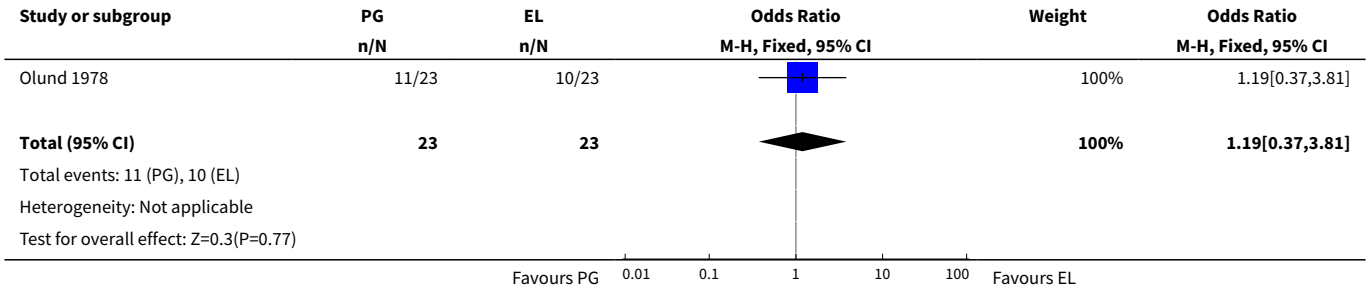
Analysis 23.3. Comparison 23 Comparison: prostaglandin versus ethacridine lactate, Outcome 3 Blood loss.



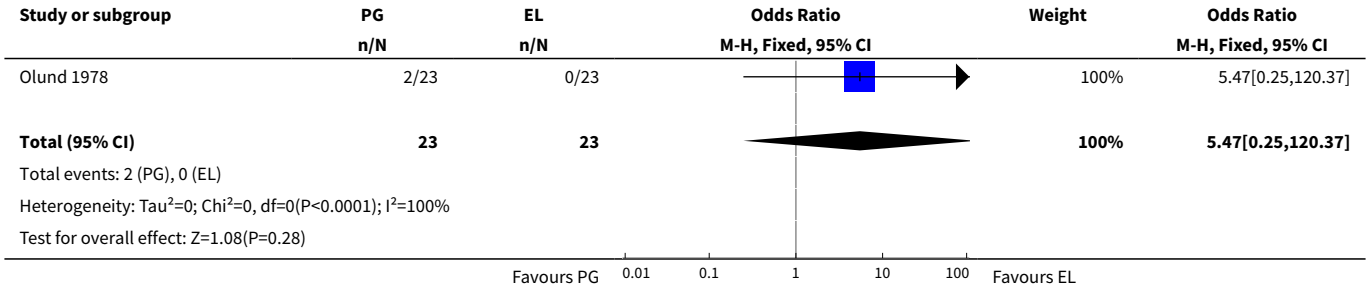
Analysis 23.4. Comparison 23 Comparison: prostaglandin versus ethacridine lactate, Outcome 4 Nausea.



Analysis 23.5. Comparison 23 Comparison: prostaglandin versus ethacridine lactate, Outcome 5 Vomiting.



Analysis 23.6. Comparison 23 Comparison: prostaglandin versus ethacridine lactate, Outcome 6 Diarrhoea.



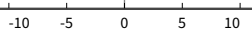
Comparison 24. Comparison: ethacridine lactate versus normal saline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction to abortion interval	1	37	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-4.02, 3.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Blood loss (need for blood transfusion)	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.26]
3 Pain (use of analgestics)	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.89]
4 Vomiting (use of antimetics)	1	40	Odds Ratio (M-H, Fixed, 95% CI)	6.33 [0.67, 60.16]
5 Uterine rupture	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.26]

Analysis 24.1. Comparison 24 Comparison: ethacridine lactate versus normal saline, Outcome 1 Induction to abortion interval.

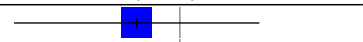
Study or subgroup	EL N	EL Mean(SD)	Normal saline N	Normal saline Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Zauva 1989	19	17.2 (4.6)	18	17.5 (6.7)		100%	-0.3[-4.02,3.42]
Total ***	**19**		**18**			**100%**	**-0.3[-4.02,3.42]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.16(P=0.87)							



Favours EL — Favours normal saline

Analysis 24.2. Comparison 24 Comparison: ethacridine lactate versus normal saline, Outcome 2 Blood loss (need for blood transfusion).

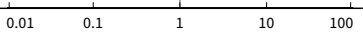
Study or subgroup	EL n/N	Normal saline n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Zauva 1989	0/20	1/20		100%	0.32[0.01,8.26]
Total (95% CI)	**20**	**20**		**100%**	**0.32[0.01,8.26]**
Total events: 0 (EL), 1 (Normal saline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					



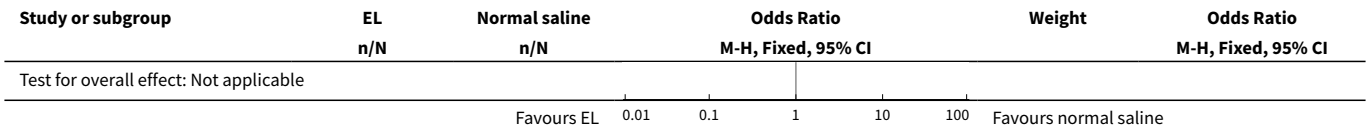
Favours EL — Favours normal saline

Analysis 24.3. Comparison 24 Comparison: ethacridine lactate versus normal saline, Outcome 3 Pain (use of analgestics).

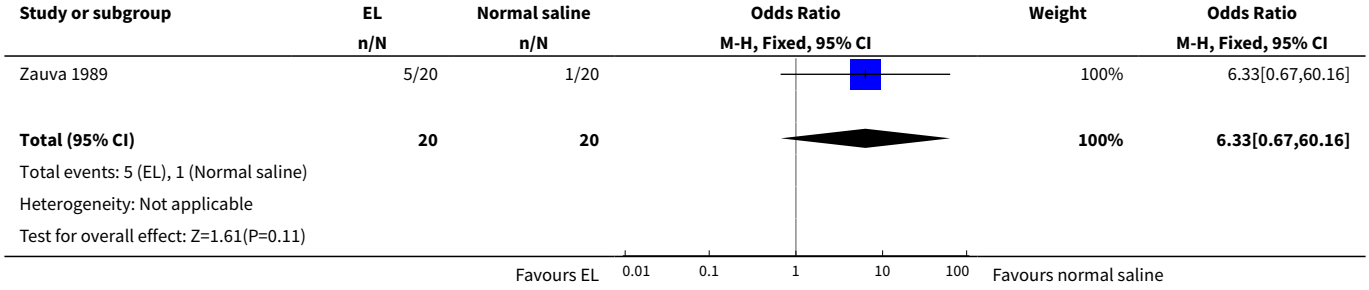
Study or subgroup	EL n/N	Normal saline n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Zauva 1989	2/20	2/20		100%	1[0.13,7.89]
Total (95% CI)	**20**	**20**		**100%**	**1[0.13,7.89]**
Total events: 2 (EL), 2 (Normal saline)					
Heterogeneity: Not applicable					



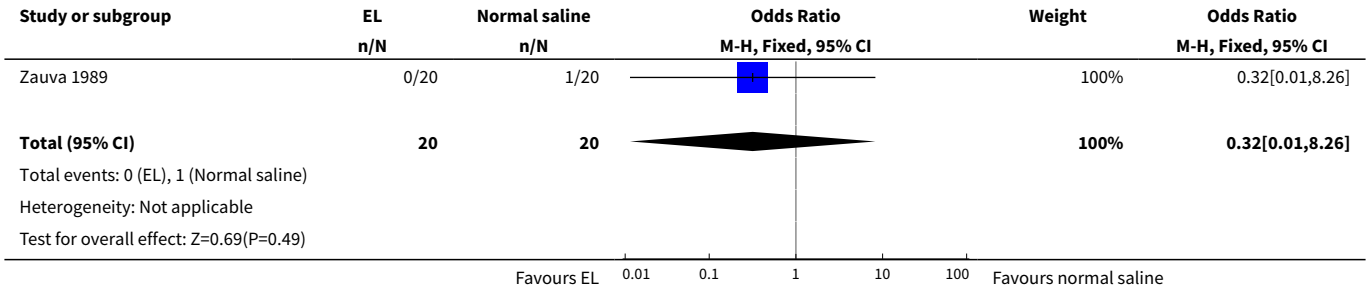
Favours EL — Favours normal saline



Analysis 24.4. Comparison 24 Comparison: ethacridine lactate versus normal saline, Outcome 4 Vomiting (use of antimetics).



Analysis 24.5. Comparison 24 Comparison: ethacridine lactate versus normal saline, Outcome 5 Uterine rupture.



CONTRIBUTIONS OF AUTHORS

HIJ Wildschut: study design, writing, editing and overall supervision

MI Both: literature search, data analyses and writing

S Medema: literature search and data management

E Thomee: data management

MF Wildhagen: statistics

N Kapp: review design, writing, editing and critical evaluation

DECLARATIONS OF INTEREST

None declared

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

NOTES

None

INDEX TERMS

Medical Subject Headings (MeSH)

Abortifacient Agents [*administration & dosage] [adverse effects]; Abortion, Induced [*methods]; Administration, Intravaginal; Drug Administration Schedule; Drug Therapy, Combination; Mifepristone [*administration & dosage]; Misoprostol [*administration & dosage] [adverse effects]; Pregnancy Trimester, Second; Prostaglandins A [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy