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Medical methods for first trimester abortion (Review)

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[Intervention Review]

Medical methods for first trimester abortion

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ABSTRACT

Background

Surgical abortion by vacuum aspiration or dilatation and curettage has been the method of choice for early pregnancy termination since the 1960s. Medical abortion became an alternative method of first trimester pregnancy termination with the availability of prostaglandins in the early 1970s and anti-progesterones in the 1980s. The most widely researched drugs are prostaglandins (PGs) alone, mifepristone alone, methotrexate alone, mifepristone with prostaglandins and methotrexate with prostaglandins.

Objectives

To compare different medical methods for first trimester abortion.

Search methods

The Cochrane Controlled Trials Register, MEDLINE and Popline were systematically searched. Reference lists of retrieved papers were also searched. Experts in WHO/HRP were contacted.

Selection criteria

Types of studies
Randomised controlled trials comparing different medical methods for abortion during first trimester (e.g. single drug, combination) were considered. Trials were assessed and included if they had adequate concealment of allocation, randomisation procedure and follow-up. Women, pregnant during the first trimester, undergoing medical abortion were the participants. The outcomes were mortality, failure to achieve complete abortion, surgical evacuation, ongoing pregnancy at follow-up, time until passing of conceptus, blood transfusion, side effects and women's dissatisfaction with the procedure.

Data collection and analysis

Two reviewers independently selected trials for inclusion from the results of the search strategy described previously.The selection of trials for inclusion in the review was performed independently by two reviewers after employing the search strategy described previously. Trials under consideration were evaluated for appropriateness for inclusion and methodological quality without consideration of their results. Data were processed using Revman software.

Main results

Fifty-eight trials were included in the review. The effectiveness outcomes below refer to 'failure to achieve complete abortion' with the intended method unless otherwise stated. 1) Combined regimen mifepristone/prostaglandin: Mifepristone 600 mg compared to 200 mg shows similar effectiveness in achieving complete abortion (4 trials, RR 1.07, 95% CI 0.87 to 1.32). Misoprostol administered orally is less effective (more failures) than the vaginal route (RR 3.00, 95% CI 1.44 to 6.24) and may be associated with more frequent side effects such as nausea and diarrhoea. Sublingual and buccal routes were similarly effective compared to the vaginal route, but had higher rates of side effects. 2) Mifepristone alone is less effective when compared to the combined regimen mifepristone/prostaglandin (RR 3.76 95% CI 2.30 to 6.15). 3) Five trials compared prostaglandin alone to the combined regimen (mifepristone/prostaglandin). All but one reported higher effectiveness with the combined regimen. The results of these studies could not be combined but the RR of failure with prostaglandin alone is reportedly between 1.4 to 3.75 with the 95% confidence intervals indicating statistical significance. 4) In one trial comparing gemeprost 0.5 mg with misoprostol 800 mcg, misoprostol was more effective (failure with gemeprost: RR 2.86, 95% CI 1.14 to 7.18). 5) There was no difference in effectiveness with use of a divided dose compared to a single dose of prostaglandin. 6) Combined regimen methotrexate/prostaglandin demonstrates similar rates of failure to complete abortion when comparing intramuscular to oral methotrexate administration (RR 2.04, 95% CI 0.51 to 8.07). Similarly, day 3 vs. day 5 administration of prostaglandin following methotrexate administration showed no significant differences (RR 0.72, 95% CI 0.36 to 1.43). One trial compared the effect of tamoxifen vs. methotrexate and no statistically significant differences were observed in effectiveness between the groups.

Authors' conclusions

Safe and effective medical abortion methods are available. Combined regimens are more effective than single agents. In the combined regimen, the dose of mifepristone can be lowered to 200 mg without significantly decreasing the method effectiveness. Vaginal misoprostol is more effective than oral administration, and has less side effects than sublingual or buccal. Some results are limited by the small numbers of participants on which they are based. Almost all trials were conducted in settings with good access to emergency services, which may limit the generalizability of these results.

PLAIN LANGUAGE SUMMARY

Medical methods for early termination of pregnancy can be safe and effective

There are several different surgical techniques for abortion during the first three months. Several drugs can also be prescribed alone or in combination to terminate early pregnancy. This is called medical abortion, and uses the hormones prostaglandins and/or mifepristone (an antiprogesterone often called RU486), and/or methotrexate. This review of trials found that medical methods for abortion in early pregnancy can be safe and effective, with the most evidence of effectiveness for a combination of mifepristone and misoprostol (a prostaglandin). Almost all of the trials were done in well-resourced settings where women returned for a check-up.

BACKGROUND

Up to 42 million abortions are performed each year (Sedgh 2007). Medical abortion has the potential to expand abortion services, where surgical services are limited, and to expand women's choice of abortion method and experience.

Surgical abortion by vacuum aspiration or dilatation and curettage has been the method of choice for early pregnancy termination since the 1960s. Medical abortion became an alternative method of first trimester pregnancy termination with the availability of prostaglandins in the early 1970s followed by the development of an antiprogesterone in the 1980s. Large uncontrolled studies suggested that early medical abortion with mifepristone and a prostaglandin would be an effective method for pregnancy termination (Urquhart 1997).

Various drugs have been used for first trimester medical abortion. The most widely researched are prostaglandins (PGs) alone, mifepristone alone, methotrexate alone, mifepristone with prostaglandins and methotrexate with prostaglandins. Prostaglandins soften the cervix, cause uterine contractions and are used orally or vaginally for ripening of the cervix before surgical or for medical abortion. The most commonly used prostaglandins are gemeprost given vaginally and misoprostol administered either orally (including buccal and sublingual) or vaginally. Misoprostol is a prostaglandin analogue registered for use in nonsteroidal anti-inflammatory drug (NSAID) induced gastric ulcer prevention and treatment. It has a strong uterotonic effect and is used to induce pregnancy terminations illegally in some parts of the world (Blanchard 1999, Costa 1998) as well as legally, in areas where mifepristone is not available. The reported complete abortion rate for misoprostol alone varies between 61% for single and 93% for repeat doses (Bugalho 1996, Carbonell 1997b). Gemeprost used alone appears to be less effective in inducing complete abortion than when used in combination with mifepristone (Norman 1992).

Mifepristone, an antiprogestogen, blocks the receptors for progesterone and glucocorticosteroid and increases the sensitivity of the uterus to prostaglandins (Bygdeman 1985). This blockage results in the breakdown of maternal capillaries in the decidua, the synthesis of prostaglandins by the epithelium of decidual glands and inhibition of prostaglandin dehydrogenase (WHO 1997).

Mifepristone has been licensed in France and China since 1988, in Great Britain in 1991 and, in the USA and India in 2000 and 2002, respectively. Mifepristone given alone has been shown to result in abortion only in 60-80% of cases, depending on the gestational age and the dose given (WHO 1997). However, in combination with a prostaglandin at up to 63 days of amenorrhoea, it leads to complete abortion in about 95% of pregnancies (United 1990) or more. The effect of mifepristone develops over a time period of 24-48 hours; therefore, prostaglandins have usually been administered after 36-48 hours. Currently, different regimens are in use. The recommended regimen by the manufacturer is mifepristone 600 mg followed by misoprostol (between 400 - 800 mcg) or gemeprost (0.5 - 1 mg vaginally) and is registered for abortion in pregnancies up to 49 days in France and up to 63 days of amenorrhoea in Great Britain. However, a reduced dose of mifepristone combined with a prostaglandin has similar effectiveness and has the advantage of being much less expensive (WHO 1997).

Methotrexate has been used successfully for the treatment of unruptured tubal pregnancy. It is a folic acid antagonist which inhibits purine and pyrimidine synthesis and is cytotoxic to the trophoblast. The use of methotrexate with misoprostol for first trimester abortion was first introduced in 1993 (Creinin 1993, Grimes 1997). This combination was more effective when misoprostol was administered 7 days after methotrexate as compared to 3 days, leading to a complete abortion rate of 98% (Creinin 1995 M800pv).

Side-effects of medical methods are heavy bleeding, pain, nausea, vomiting and diarrhoea, varying in severity according to the protocols and gestational age (Henshaw 1994). In two randomised controlled trials included in the Cochrane review of the subject, compared to surgical procedures, medical methods are associated with a longer duration of bleeding (Say 2002, updated 2010).

Failed abortion is an infrequent but important complication of medical abortion. Both methotrexate and misoprostol may lead to fetal anomalies if the pregnancy persists, as described by some (Grimes 1997). However, other reports state that none of the malformations reported could be conclusively related to medications used for medical abortion (Wiebe 2006).

Some women prefer medical to surgical abortion. 'More natural', 'being easier', more private', and 'can be done earlier in pregnancy' were reasons to opt for a medical method by some women (Creinin 1996b). Characteristics such as the method being more new, less invasive and the possibility of verifying the expulsion were reported by others (Bachelot 1992).

Medical methods for first trimester abortion are already widely available in some countries and increasingly available throughout the world. It is therefore important to identify the best available agents and regimen for use. Comparison of medical methods with surgical evacuation in the first trimester is the subject of another review: Say 2002, updated 2010.

OBJECTIVES

To compare different medical methods for first trimester abortion.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing different medical methods (e.g. single drug, combination), ways of application, or different dose regimens, single or combined, for medical abortion, were considered. Trials were not excluded based on an arbitrary cut-off limit regarding losses to follow-up. Trials were excluded if there were unexplained imbalances in different groups at follow-up and from available outcome data.Trials were assessed and included if they had adequate concealment of allocation, randomisation and follow-up.

Types of participants

Women, pregnant in the first trimester, undergoing medical abortion.

Types of interventions

Different medical methods used for first trimester abortion, compared with each other or placebo. See 'Search methods for identification of studies' for a list of pharmaceutical preparations.

Types of outcome measures

The main outcome measure was failure to achieve complete abortion. Surgical evacuation (as emergency procedure, non-emergency procedure, or undefined), ongoing pregnancy at follow-up, time until passing of conceptus (> 3-6 hours), blood transfusion, blood loss (measured or clinically relevant drop in haemoglobin), days of bleeding, pain resulting from the procedure (reported by the women or measured by use of analgesics), additional uterotonics used, women's dissatisfaction with the procedure, nausea, vomiting, and diarrhoea were also assessed. Although mortality is considered an important outcome we did not anticipate analyzing abortion-related mortality within the context of these trials.

Search methods for identification of studies

The Cochrane Controlled Trials Register, MEDLINE and Popline were systematically searched. Reference lists of retrieved papers were also searched. Electronic literature search of MEDLINE (with the Cochrane 3-stage search strategy)(1966-2003) and POPLINE (1970-2003) databases with the following key words: (abortion OR pregnancy termination OR termination of pregnancy) AND (first trimester OR early) AND (mifepristone OR misoprostol OR methotrexate OR dinoprost* OR carboprost OR sulprostone OR gemeprost OR meteneprost OR lilopristone OR onapristone OR epostane OR oxytocin OR RU 486 OR mifegyne). There were no language preferences in the application of the search.

Data collection and analysis

The selection of trials for inclusion in the review was performed independently by two reviewers after employing the search strategy described previously. Trials under consideration were evaluated for appropriateness for inclusion and methodological quality without consideration of their results. A quality score for concealment of allocation has been assigned to each trial, using the criteria described in the Cochrane Handbook:

(A) adequate concealment of the allocation
(B) unclear whether adequate concealment of the allocation
(C) inadequate concealment of allocation (includes quasi-randomised studies)
(D) allocation concealment not used
Only trials scoring A or B were included in the review.

Failure to achieve complete abortion is defined as an abortion which is not completed by the described intended method. Other outcomes are failure of expulsion after 4 - 6 hours, side effects (nausea, vomiting, diarrhoea, abdominal pain), and mean duration of days of bleeding. A further division into early (≤ 49 days of amenorrhoea) and late (> 49 days) gestational age at the time of abortion was made for subgroup analysis. Complications are defined as any serious complication described by the authors and which was not a failure or side effect.

A form was designed to facilitate the process of data extraction which has been performed by two of the reviewers independently. In case of discrepancies between reviewers in either the decision of inclusion/exclusion of studies or in data extraction, this was resolved by consensus. Attempts were made to obtain additional information from authors if required.
Whether or not an "intention-to-treat" analysis was done in the primary study was examined.

Data were processed using RevMan software. For reasons of clarification some coding was added to some trials included in the meta-analysis: GP -gemeprost, the number next to it - refers to the dose of gemeprost in grams, M - misoprostol, the number next to it - refers to the dose in mcg, MP - minprostin, the number next to it refers to the dose in mg, PGF2 - Prostaglandin F2alpha; PGE1- prostaglandin E1 analogue; MI - mifepristone - the number next to it refers to the dose in mg; MT - methotrexate, T - testosterone propionate, TM - tamoxifen; po - oral and pv - vaginal administration.

Results are presented as relative risk and 95% confidence interval (RR; 95%CI) using the fixed effects model. If a large I^2 was found in the pooled analysis, a random effects model was applied and the tau ^{2} value was evaluated for possible heterogeneity and reported if present.

Subgroup analyses were performed where possible for early and late first trimester abortions as the performance of some methods may differ with gestational age: 1) abortion up to 49 days, 2) abortion > 49 days of amenorrhoea.
The studies in this field use various combinations of agents, doses, intervals between the antiprogesterone and prostaglandin, and route of administration for prostaglandin. Since all of these variables may affect the outcomes, it was not considered appropriate to combine similar trials into meta-analysis in many cases. However, it was possible to identify an experimental intervention and a constant (fixed) intervention which enabled us to group the trials as follows:

Combined regimen mifepristone/prostaglandin:

- Intervention: dose of mifepristone (comparison 1)
- Intervention: dose of prostaglandin (comparison 2)
- Intervention: type of prostaglandin (comparison 3)
- Intervention: timing of prostaglandin (comparison 4)
- Intervention: misoprostol oral versus vaginal (comparison 5)
- Intervention: misoprostol buccal versus vaginal (comparison 6)
- Intervention: misoprostol buccal versus oral (comparison 7)
- Intervention: misoprostol sublingual versus vaginal (comparison 8)
- Intervention: misoprostol sublingual versus oral (comparison 9)
- Intervention:single versus split dose prostaglandin (comparison 10)
- Intervention: single versus repeated prostaglandin (comparison 11)
- Mifepristone alone versus combined regimen mifepristone/ prostaglandin (comparison 12)
- Prostaglandin alone versus a combined regimen (all) (comparison 13)

Single regimen:

- Prostaglandin alone: route of administration (comparison 14)

- Mifepristone single regimen - high versus low dose (comparison 15)

Combined regimen methotrexate/prostaglandin:

- Intervention: timing of prostaglandin (comparison 16)
- Intervention: route of methotrexate: intramuscular versus oral (comparison 17)
- Intervention: dose of methotrexate (comparison 18)
- Intervention: route of prostaglandin (comparison 19)

Tamoxifen versus methotrexate (combined with prostaglandin):

- Intervention: low dose tamoxifen (40 mg)(comparison 20)
- Intervention: high dose tamoxifen (160 mg) (comparison 21)

Combined regimen mifepristone/prostaglandin versus mifepristone/prostaglandin plus tamoxifen (comparison 22)

RESULTS

Description of studies

see table: Characteristics of included studies

Risk of bias in included studies

Thirty-five trials scored adequate allocation concealment (A) and in 23 trials allocation concealment was unclear (B).Two trials used an open-label design (Schaff 2000 MI200M800, Schaff 2001 M800MI200).
Two of the trials mentioned performing an 'intention -to -treat analysis' (WHO 2000 M400po, WHO 2001 GP1pv).

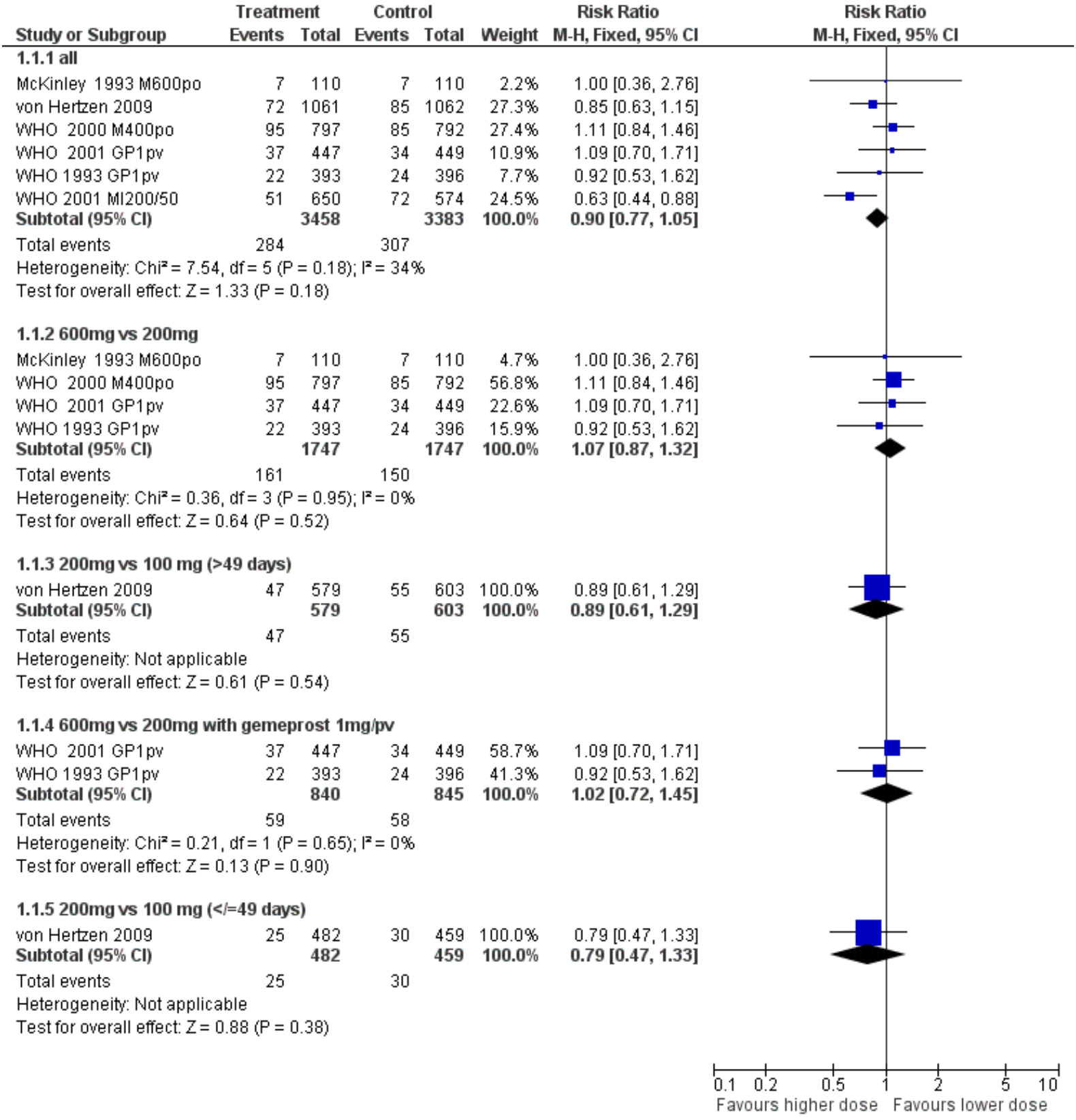
Effects of interventions

Fifty-eight trials are included in this review. Due to the many different interventions, trials were grouped into comparisons, as listed below. The main outcome for which the meta-analyses were performed was failure to achieve complete abortion with the method intended. Data on side-effects could be combined for some comparisons. Major complications with any of the methods were rarely reported and if so, they are listed in the tables of Characteristics of included studies. Data are presented for different gestational ages where possible (≤ 49 days, > 49 days). One trial presented its data in two different publications (Honkanen 2004, von Hertzen 2003). One trial used 2 different comparisons, and is therefore listed as 2 different trials (Wiebe 1999 and Wiebe 1999 A). Six studies used different regimens/doses/timing of the drugs that could not be combined with any of the other regimens in the compraisons and are therefore listed separately inTable 1 (Wang 2000, Arvidsson 2005, Wiebe 2006, Liao 2004, WHO 1989, WHO 1991).

Our main outcome was failure to achieve complete abortion with the method intended. Fourteen trials used either other definitions (i.e. surgical intervention) or administered additional prostaglandins (Carbonell 1997 M800pv, Creinin 1994 M800&MT, Creinin 1995 M800pv, Creinin 1996 M800pv, Creinin 1997 M800pv, Creinin 2001 MI600 M400, Jain 1999 M800&TM, Ozeren 1999 MP800&MT, Koopersmith 1996, Schaff 2000 MI200M800, Wiebe 1999 A, Wiebe 1999 B, Hamoda 2005). We conducted sensitivity analysis when appropriate to present the results accordingly.

Combined regimen mifepristone/prostaglandin
Intervention: dose of mifepristone: (comparison 1; Figure 1 *)*

Figure 1. Forest plot of comparison: 1 combined regimen mifepristone/prostaglandin: dose of mifepristone, outcome: 1.1 failure to achieve complete abortion.



There are nine trials included, six are included in the meta-analysis. The comparisons are 600mg versus 200mg, 200mg versus 100mg, and 200mg versus 50mg of mifepristone (McKinley 1993 M600po, WHO 1993 GP1pv WHO 2000 M400po, WHO 2001 MI200/50, WHO 2001 GP1pv, von Hertzen 2009). Three trials used split doses of mifepristone and are presented in the additional tables (WHO 1989, WHO 1991, Liao 2004).

All trials: Failure to achieve complete abortion was similar between higher versus the lower dose mifepristone groups (0.90 95%CI 0.77 to 1.05). Analysis 1.1

600mg versus 200 mg: There are 6 (McKinley 1993 M600po; WHO 1989, WHO 1991, WHO 1993 GP1pv, WHO 2000 M400po, WHO 2001 GP1pv) trials included in the review, of which data from 4 trials with overall 3482 women were included in the meta-analysis (McKinley 1993 M600po; WHO 1993 GP1pv, WHO 2000 M400po, WHO 2001 GP1pv). McKinley used misoprostol 600mcg/po, WHO trials (WHO 1993 GP1pv and WHO 2001 GP1pv) used gemeprost 1mg/pv or misoprostol 400mcg/po (WHO 2000 M400po). There was no difference in failure to achieve complete abortion between 200 mg and 600 mg of mifepristone (RR 1.07 95% CI 0.87 - 1.32). The pooled analysis of the two trials using the same dose and type of prostaglandin (gemeprost 1mg) showed no difference for failure rates (RR 1.02 95%CI 0.72 to 1.45). Time until passing of conceptus >3-6 hours was similar for the two groups in the three trials reporting on it. The four trials reporting on ongoing pregnancy at follow -up

(Liao 2004, McKinley 1993 M600po, von Hertzen 2009, WHO 1993 GP1pv) showed no statistically significant difference between the two groups. These trials used different types and doses of misoprostol and the results are therefore presented for each trial individually. Side effects were similar between the two groups.

200mg versus 100 mg: One trial was included in this comparison (von Hertzen 2009.) This was a four-arm trial, comparing 100 vs 200 mg of mifepristone followed by 800mcg misoprostol/pv after 24 or 48 hours. Failure rates were similar between the groups.

200mg versus 50 mg: WHO (WHO 2001 MI200/50) used 200 or 50 mg followed by 0.5 or 1 mg of gemeprost/pv. The group receiving mifepristone 50mg and gemeprost 0.5 mg was discontinued after 249 participants were enrolled because the complete abortion rate was below the pre-determined cut off. Women receiving 200 mg of mifepristone were less likely to have failure in achieving complete abortion (RR 0.63 95%CI 0.44 to 0.8) and had fewer ongoing pregnancies at follow-up (RR 0.20 95%CI 0.07 to 0.58).

Combined regimen mifepristone/prostaglandin

Intervention: dose of prostaglandin (comparison 2, Analysis 2.1 *)*

Six trials are included in the review, the data from four of them could be included in the meta-analysis. Two of these trials (Rodger 1989 MI600, WHO 2001 MI200/50) compared gemeprost 1 mg versus gemeprost 0.5 mg in 1284 women. There were fewer failures with the 1 mg dose but the difference did not reach statistical significance (RR 0.75, 95% CI 0.54 to 1.05). The largest trial in this comparison (WHO 2001 MI200/50) used a factorial design (mifepristone 50/200 mg and gemeprost 1/0.5 mg). Looking at the group with mifepristone 200 mg only, the difference between the two doses of gemeprost is less significant (RR 0.81, 95% CI 0.45 to 1.43). The arm with the smallest dose (mifepristone 50 mg and gemeprost 0.5 mg) was stopped prematurely after 249 women were enrolled, as the effectiveness was below the predetermined cut-off point. Rodger (Rodger 1989 MI600) included 120 women in the study. The first 60 women were not randomised; therefore only data for the second 60 women are included in this review.

Two trials compared different doses of oral misoprostol after 200 mg of mifepristone. Coyaji 2007 compared misoprostol 400mcg to 800mcg (given orally; 800mcg was administered as a repeat dose of 400mcg after 3 hours). Shannon 2006 used 3 groups, comparing misoprostol 400mcg, 600mcg and 800mcg. Data from the 400mcg and 800mcg groups were included in the review. The failure rates and side effects were similar between the groups. There were fewer ongoing pregnancies in the 800mcg compared to the 400mcg group (0.10 95%CI 0.01 to 0.76). Side effects were similar between the groups.

Combined regimen mifepristone/prostaglandin

Intervention: type of prostaglandin (comparison 3, Analysis 3.1 *)*

1)gemeprost versus misoprostol

Two trials are included (Baird 1995 GP0.5 M600po, Bartley 2001 GP0.5M800pv) using different doses of misoprostol and different routes of administration. Therefore the results were not combined in a meta-analysis. However, when misoprostol is used at a higher dose (800 mcg) and administered vaginally, it appears to be more effective than gemeprost 0.5 mg (RR 2.86 95%CI 1.14 to 7.18), according to data from a single trial (Bartley 2001 GP0.5M800pv). Vomiting and diarrhoea were more common with misoprostol compared to gemeprost (RR 1.49 95%CI 1.06 to 2.10; RR 2.66 95%CI 1.35 to 5.26). There was no difference for other outcomes, such as ongoing pregnancy and time until passing of conceptus > 3-6 hours between the groups.

2)PGF2 alpha versus misoprostol

There was no difference in efficacy when comparing PGF2 alpha to misoprostol 600 mcg orally (Sang 1994 M600poPGF2pv, Sang 1999 M600poPGF2pv).

Combined regimen mifepristone/prostaglandin

Intervention: timing of prostaglandin (comparison 4, Analysis 4.1 *)*

There are six trials included for this comparison. Three trials used different dose regimens as well as time intervals; therefore, the results are presented for each trial separately. Misoprostol administered on day 3 following mifepristone seems to be less effective in achieving complete abortion when compared to day 1 in the one trial reporting on it (Schaff 2000 MI200M800). The follow-up for all women was on day 8 after mifepristone. There were 53 women in the sample who received additional misoprostol if the gestational sac was present at the first follow-up visit. It is not clear how these women were distributed by treatment group. There was no difference between the groups with regard to need for surgical evacuation, ongoing pregnancy or women's dissatisfaction with the method. No difference regarding failure rate was shown in one trial when comparing day 3 versus day 2 (Schaff 2000 MI200M800). Two trials compared misoprostol on 2 versus day 0 (Creinin 2001 MI600 M400; Guest 2007). Creinin used mifepristone 600mg followed by misoprostol 400mcg; Guest used mifepristone 200mg followed by misoprostol 800mcg. Failure to achieve complete abortion was lower when misoprostol was administered 36 -48 hours compared to 6 hours after mifepristone (RR 0.39 95%CI 0.24 to 0.65). There was no difference in the occurrence of side effects (nausea, vomiting, diarrhoea) between the 2 groups. Two trials (Creinin 2004, Creinin 2007) used the same dose and route. Mifepristone 200mg followed by misoprostol

800mcg pv administered on day 1 was more effective than administration ≤ 6h later (RR 0.65 95%CI 0.46 to 0.92). In the comparison of misoprostol day 2 versus day 1, failure to achieve complete abortion rates were similar when combining results for gestational ages up to 63 days. However, failure rates were higher with misoprostol administered on day 2 compared to day 1 in women > 49 days of gestation based on one trial (von Hertzen 2009) (RR 1.62 95%CI 1.11 to 2.38), not in three studies, when all days of gestation were considered (Sandstrom 1999 MI600GP1pv, Schaff 2000 MI200M800, von Hertzen 2009).

Combined regimen mifepristone/prostaglandin: route of administration for misoprostol

Intervention : misoprostol oral versus vaginal (comparison 5, Analysis 5.1)

Six trials are included in the review, 2 trials with a total of 1407 women are included in the meta-analysis (El-Refaey 1995 M800MI600; Schaff 2000 MI200M800). El-Refaey used mifepristone 600mg and Schaff used mifepristone 200mg. Both used misoprostol 800mcg orally or vaginally after 48 hours (El-Refaey) and at least 24 hours (Schaff) after mifepristone. A statistically significant higher number of women had failure to achieve complete abortion when misoprostol was administered orally (RR 3.05 95% CI 1.98 to 4.70). Nausea and diarrhoea occurred more often in the group receiving misoprostol orally (RR 1.13 95% CI 1.02 to1.25; RR 1.80 95% CI 1.49 to 12.18, respectively). Unexpectedly, vomiting occurred more often in the vaginal group in one trial (Schaff 2001 M800MI200), and reporting error cannot be excluded. Three trials used different doses orally and vaginally and were therefore not included in the meta-analysis (Creinin 2001 and Shannon 2006, Arvidsson 2005). In one trial (Shannon 2006), failure to achieve complete abortion was similar among those who recieved a lower dose (400 mcg) of oral misoprostol than those who received 800 mcg of vaginal misoprostol; however, women were instructed to repeat their misoprostol dose at home one day following the first misoprostol dose in case of scant bleeding, and 28% did so. In 2005, Arvidsson (Arvidsson 2005) reported only on side effects and women's satisfaction (data included in additional tables) following use of either oral or vaginal misoprostol. Tang (Tang 2002) used a combined regimen oral/vaginal in one group and repeated oral misoprostol doses in another group, and these data were therefore not included in the meta-analysis.

Intervention : misoprostol buccal versus vaginal (comparison 6, Analysis 6.1)

One trial (Middleton 2005) was included for this comparison. Failure to achieve complete abortion was similar in both groups. There were statistically significantly more women with diarrhoea in the buccal compared to the vaginal group (RR 1.51 95%CI 1.12 to 2.03).

Intervention : misoprostol buccal versus oral (comparison 7, Analysis 7.1)

One trial (Winikoff 2008) is included in this comparison. The failure rate was lower in the buccal group (0.45 95%CI 0.25 to 0.79) for all gestational ages and for women with > 49 days of gestation (RR 0.37 95%CI 0.18 to 0.73). The failure rates were similar between the two groups for women ≤ 49 days. Overall ongoing pregnancy rate was lower in the buccal group (RR 0.27 95%CI 0.09 to 0.82) and for women > 49 days of gestation (RR 0.18 95% CI 0.04 to 0.78), while rates were similar for women with gestations ≤ 49 days. Fewer women in the oral group had nausea compared to the buccal group (RR 1.10 95% CI 1.01 to 1.19). Women reported similar rates of satisfaction between the two groups.

Intervention : misoprostol sublingual versus vaginal (comparison 8, Analysis 8.1)

Two trials were included in this comparison (Hamoda 2005, Tang 2003). There was no difference in failure rates or in number of needed surgical evacuations. In one trial (Hamoda 2005) women received additional doses of misoprostol if abortion was incomplete at follow-up and the results were not presented for the intended method used and were therefore not totaled. Tang 2003 reported that significantly more women in the sublingual group experienced side-effects: nausea (RR 1.67 95%CI 1.21 to 2.29), vomiting (RR 2.93 95% CI 1.69 to 5.06), diarrhoea (RR 2.5 95%CI 1.55 to 4.04). More women were dissatisfied with the method in the one trial reporting on it (Hamoda 2005)(RR 2.81 95%CI 1.15 to 6.87) compared to the vaginal group. Hamoda did not use an intention to treat analysis; loss to follow up was identical in both groups (n=13).

Intervention : misoprostol sublingual versus oral (comparison 9, Analysis 9.1)

One trial was included in this comparison (Raghavan 2009). Women in the sublingual group were less likely to fail to achieve complete abortion compared with the oral group (RR 0.21 95%CI 0.06 to 0.72). More women were dissatisfied with the procedure in the sublingual group; however, this difference did not reach statistical significance (RR 1.96 95%CI 0.94 to 4.09). Side effects were similar among the two groups.

Combined regimen: mifepristone/prostaglandin

Intervention: single versus split dose of prostaglandin (comparison 10, Analysis 10.1)

One trial was included in this comparison (El-Refaey 1994). There was no statistically or clinically significant difference between administration of 800 mcg of misoprostol as a single dose or by 2 doses of 400 mcg, 2 hours apart (RR 0.70 95% CI 0.21 - 2.39) regarding failure rates. The side-effects tended to favour the split-dose group but were not statistically significant different between the 2 groups.

Intervention: single versus continuous misoprostol (comparison 11, Analysis 11.1)

Two trials are included (Tang 2002, von Hertzen 2003). Honkanen 2004 reports on the same trial as von Hertzen 2003, but on different outcomes. Both trials compared oral misoprostol 400 mcg twice daily continued for 7 days after either an initial oral (group A) or vaginal 800mcg (group B) and single vaginal dose (group C) among 150 women. All women had received mifepristone 200mg 48 hours prior to misoprostol. More women failed to achieve complete abortion in the all oral group (A) compared to the vaginal and continuous oral misoprostol group (B) (RR 1.60 95%CI 1.00 to 2.57). When analysed by subgroups of gestational age, the difference was present in women > 49 days of gestation (RR 1.48 95%CI 1.01 to 2.16) but not in women ≤ 49 days. More women in the all oral group (A) had diarrhoea compared to the vaginal & continuous oral group and single vaginal group (RR 1.83 95%CI 1.11 to 3.01 group B and RR 2.09 95%Ci 1.24 to 3.53 group C). There was no difference with regard to nausea or vomiting and number of days of bleeding, reported as median and range (Tang 2002): group A: 16 (8-107), group B:15

(8-65), group C:16(8-74) and as median: 13 days (group A), 12 days (group B) and 12 days (group C) (Honkanen 2004).

Intervention: Mifepristone alone versus mifepristone/prostaglandin (comparison 12, Analysis 12.1 *)*
Three trials were included in this comparison: compared to the combination regimen, mifepristone alone was significantly less effective (RR of failure 3.76 95% CI 2.30 - 6.15) (Cameron 1986 MI600GP1pv, Swahn 1989 MI200MP1po, Zheng 1989 MI600PGF2pv).

Prostaglandin alone versus a combined regimen (all) (comparison 13, Analysis 13.1)
Six trials were included in this comparison (Cheng 1994 PGE1&T, Creinin 1994 M800&MT, Jain 1999 M800&TM, Jain 2002 M800&MI, Ozeren 1999 MP800&MT, Wiebe 2006). Wiebe 2006 compared methotrexate combined with 400mcg misoprostol vaginal or misoprostol 400mcg sublingual or 400mcg vaginal and was not included in the meta-analysis, but data are presented in the additional table. One trial used additional doses of prostaglandin and did not specify which women received them (Jain 1999 M800&TM). The studies consistently demonstrate that compared to a combination regimen, misoprostol alone was significantly less effective in achieving complete abortion (2.50 95%CI 1.89 to 3.32). The analysis, excluding the Jain 1999 M800&TM trial showed similar results (RR 2.40 95%CI 1.79 to 3.20).
There was less nausea with misoprostol only compared to the combined regimen in the 3 trials reporting on it (nausea RR 0.71 95%CI 0.56 - 0.88) (Creinin 1994 M800&MT, Ozeren 1999 MP800&MT, Jain 2002 M800&MI).

Prostaglandin alone: route of administration (comparison 14, Analysis 14.1)

One trial was included, comparing misprostol sublingual versus vaginal application, given in three doses each of 800mcg either 3 or 12 hourly. There was no difference in failure to achieve complete abortion between the groups. More women in the sublingual group had vomiting and diarrhoea compared to the vaginal group (RR1.54 95%CI 1.14 to 2.08 and RR 1.53 95%CI 1.33 to 1.76).

Mifepristone single - high versus low dose (comparison 15, Analysis 15.1 *)*
One trial was included in this comparison (Birgerson 1988). No difference between a low (140 mg) and high (700 mg) dose of mifepristone was found regarding the failure rate.

Combined regimen: methotrexate/prostaglandin
Timing of prostaglandin (comparison 16, Analysis 16.1 *)*
Three trials are included in the review (Carbonell 1997 M800pv, Carbonell 1998 M800pv, Creinin 1995 M800pv) and data from 2 trials are included in the meta-analysis (Carbonell 1997 M800pv, Carbonell 1998 M800pv).There was no significant difference in failure to achieve complete abortion between misoprostol given on day 5 compared to day 3 (RR 0.72 95% CI 0.36-1.43) or on day 5 compared to day 4 (RR 0.73 95% CI 0.37-1.48) following methotrexate.

Route of methotrexate: intramuscular versus oral (comparison 17, Analysis 17.1 *)*
One trial compared intramuscular versus oral administration of methotrexate (Wiebe 1999 B). There was no difference regarding the failure rate (RR 2.04 95% CI 0.51-8.07) or side effects (nausea: RR 0.52 95% CI 0.22-1.25; vomiting: RR 4.89 95% CI 0.57-42.21; diarrhoea: RR 1.22 95% CI 0.18-8.34).

Dose of methotrexate (comparison 18, Analysis 18.1 *)*
Two trials were eligible to be included in the review (Creinin 1996 M800pv, Creinin 1997 M800pv). Both trials had a very small sample size (10 women in each group); they used differently dosed regimens and are therefore presented separately.

Route of prostaglandin (misoprostol) (comparison 19, Analysis 19.1 *)*
One trial (Wiebe 2004) compared buccal versus vaginal administration of misoprostol 3-6 days after methotrexate. Women received additional misoprostol; it is unclear how many or in which treatment group. The vaginal route was more effective in achieving complete abortion (RR 1.43 95%CI 1.08 to 1.90). There was no difference regarding occurrence of side-effects between the groups.

Tamoxifen versus methotrexate (combined with prostaglandin):
Wiebe compared methotrexate to tamoxifen, both followed by misoprostol. The trial was conducted in 2 phases: phase 1 used low-dose tamoxifen (40 mg) and phase 2 used high- dose (160 mg). This trial has therefore been referred to as Wiebe 1999 (low dose) and Wiebe 1999 A (high dose).

Intervention: low dose tamoxifen (40 mg)(comparison 20, Analysis 20.1 *)*
There was no statistically significant difference regarding failure rates between the groups (RR 2.04 95% CI 0.86-4.84) and side-effects (nausea: RR 0.56 95% CI 0.33-0.971; vomiting: RR 1.70 95% CI 0.42-6.92; diarrhoea: RR 1.53 95% CI 0.26-8.96) in the one trial included (Wiebe 1999).

Intervention:high dose tamoxifen (160 mg) (comparison 21, Analysis 21.1 *)*
There was no statistically significant difference regarding failure rates between the 2 groups (RR 1.96 95% CI 0.93-4.15) or side-effects (nausea: RR 0.78 95% CI 0.54-1.10; vomiting: RR 0.65 95% CI 0.28-1.53; diarrhoea: RR 1.23 95% CI 0.34-4.43).

Combined regimen mifepristone/prostaglandin versus mifepristone/prostaglandin plus tamoxifen (comparison 22, Analysis 22.1)
One trial was included (Wu 1993); no statistically significant difference between the 2 groups regarding failure to achieve complete abortion was found (RR 1.29 95% CI 0.82 - 2.02).

Other comparisons:
Wang (Wang 2000) compared mifepristone 25mg/day over 7 days (total dose of 250mg) followed by oral misoprostol 200mg / day over 3 days (total dose of 1200mcg) to mifepristone 150mg on day 1 followed by oral misoprostol 600mcg on day 3. The doses and regimens in the two groups make it difficult to make any meaningful conclusion from this comparison. Koopersmith (Koopersmith 1996) compared misoprostol alone to misoprostol/ tamoxifen and misoprostol/ laminaria. The sample size was very small which preclude makinge any meaningful conclusions from this study. These 2 trials are included in the additional tables. Additionally, Blanchard 2005 used various doses, routes and time of misoprostol administered alone in a very small sample of women.

DISCUSSION

The literature on different medical abortion methods is vast, but contains relatively few randomised controlled trials comparing the different regimens. The trials included were all conducted after the mifepristone/misoprostol regimen was licensed for sale in Great Britain and France and rather sought to determine if a lower dose and less costly regimen could be as effective as the licensed one. Grimes (Grimes 1997) and Bygdeman (Bygdeman 2002) in their reviews mentioned the different aspects to be considered when using medical abortion methods.
Medical methods used are mostly combined regimens and many different types of combinations are described. To facilitate synthesising the data, trials were grouped into comparisons, as listed above. The objective of this approach was to enable the evaluation of the experimental intervention being studied trying to avoid getting lost in the endless permutations of the combinations of different components. The focus was mainly on primary outcomes, such as effectiveness, complications, side-effects and acceptability.
Meta-analysis was complicated by the use of different pharmaceutical agents, different doses and different routes of application; therefore, most meta-analyses contain only a small number of reasonably comparable trials. The review focused on the primary outcome of effectiveness; firm conclusions on associated side-effects or relatively uncommon complications, such as continuing pregnancy or haemorrhage.

These data support that the most common combined regimen (mifepristone/misoprostol) is an effective and safe method for pregnancy termination in the first trimester. The effect of mifepristone is not decreased by lowering the dose from previously recommended 600 mg to 200 mg when combined with at least 400 mcg of misoprostol. In earlier studies, it was demonstrated that the linear dose-response effect of mifepristone does not occur in doses above 100 mg (Beaulieu 1997). A combination regimen with a prostaglandin is more effective than use of prostaglandin alone. Similarly, mifepristone alone is less effective than when combined with a prostaglandin.

Different prostaglandins have been used for medical abortion, but misoprostol has superior attributes; misoprostol is at least as effective as gemeprost and is less costly, does not require refrigeration and offers different routes of administration. Of the different routes of misoprostol administration, vaginal appears to be superior to oral administration in terms of efficacy in the meta-analysis and majority of trials, and has fewer side effects when compared to oral and sublingual routes.

In regards to the role of gestational age, when comparing abortion at ≤ 7 weeks to those at 9 weeks or more, at least a doubling in the rate of failure was reported in one study (WHO 2000 M400po). There was not sufficient data to confirm these findings in this review.

Methotrexate, combined with a prostaglandin, has been used in some studies with an effectiveness of mostly > 90%. No trial comparing mifepristone/prostaglandin with methotrexate/prostaglandin was identified.

An important aspect of this review is the overall very low rate of major complications reported among the various medical abortion regimens. The most common complication is the need for blood transfusion (about 0.2%) (see table 'characteristics of included studies'). The reported self-limiting side-effects of medical abortion regimens are mainly due to the prostaglandins (nausea, vomiting, diarrhoea). The dose, route and type of prostaglandin used may influence the occurrence of side effects, as higher doses and oral administration are associated with an increase in nausea and vomiting.

The generalizability of these results to some settings may be limited, as most trials considered in the review had inclusion criteria which were strict: intrauterine pregnancy was confirmed by ultrasound, emergency back-up facilities were available and follow-up was high. Fortunately, an increasing number of studies are focusing on the provision of medical abortion outside these particular constructs, although they were not the focus of this review. Additional barriers to introduction of medical abortion may include the relatively high cost and need for registration of mifepristone.

Acceptibility with medical abortion methods is often associated with the success of the abortion, and may decrease with higher gestational ages (Honkanen 2002; Winikoff 1997; Honkanen 2004). Whether acceptability of different application routes are linked to age, parity or cultural differences is not well established. The difference in time intervals between mifepristone and methotrexate and the administration of prostaglandin, or their use outside the health-care setting may also play a role in the acceptability of one method over the other.

Other comparisons, such as tamoxifen/prostaglandin combination have not been evaluated extensively enough to draw firm conclusions. Some outcomes such as number of days of bleeding with the procedure, pain, time to return of menstruation or acceptability have not been assessed sufficiently.

AUTHORS' CONCLUSIONS

Implications for practice

The available data from this review demonstrates that the combination mifepristone/misoprostol is a safe and effective abortion method in the first trimester up to 63 days. The effectiveness is not reduced by lowering the currently licensed dose of 600 mg of mifepristone to 200mg. Data on methotrexate/prostaglandin regimen is scarce.
This review does not address introducing medical abortion where back-up facilities are not available and women are less likely to attend for the follow up.

Implications for research

Methotrexate in combination with a prostaglandin may be an alternative to the mifepristone/prostaglandin regimen in places where mifepristone is either unaffordable or unavailable. However, further research should be conducted to compare the methotrexate/prostaglandin combination regimen with the standard mifepristone/prostaglandin regimen.
There is scarce data on issues such as which method is preferable when in addressing specific side-effects, bleeding patterns, acceptability or financial impact of the different methods. Good quality acceptability studies are important to investigate the components of medical abortion regimens that affect acceptability in different settings.

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REFERENCES

References to studies included in this review

Arvidsson 2005 *{published data only}*

Arvidsson C, Hellborg M, Gemzell-Daniellson K. Preference and acceptability of oral versus vaginal administrationof misoprostol in medical abortion with mifepristone. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2005;**123**:87-91.

Baird 1995 GP0.5 M600po *{published data only}*

* Baird DT, Sukcharoen N, Thong KJ. Randomized trial of misoprostol and cervagem in combination with a reduced dose of mifepristone for induction of abortion. *Human Reproduction* 1995;**10**(6):1521-1527.

Bartley 2001 GP0.5M800pv *{published data only}*

* Bartley J, Brown A, Elton R, Baird DT. Double-blind randomized trial of mifepristone in combination with vaginal gemeprost or misoprostol for induction of abortion up to 63 days gestation. *Human Reproduction* 2001;**16**(10):2098-2102.

Birgerson 1988 *{published data only}*

* Birgerson L, Odlind V. The antiprogestational agent RU 486 as an abortifacient in early human pregnancy: a comparison of three dose regimens. *Contraception* 1988;**38**(4):391-400.

Blanchard 2005 *{published data only}*

Blanchard K, Tara Shochet T, Coyajic K, Ngoc N, Winikoff B. Misoprostol alone for early abortion: an evaluation of seven potential regimens. *Contraception* 2005;**72**:91-97.

Cameron 1986 MI600GP1pv *{published data only}*

* Cameron IT, Michie AF, Baird DT. Therapeutic abortion in early pregnancy with antiprogestogen RU 486 alone or in combination with prostaglandin analogue (gemeprost). *Contraception* 1986;**34**(5):459-468.

Carbonell 1997 M800pv *{published data only}*

* Carbonell JL, Velazco A, Varela L, Cabezas E, Fernandez C, Sanchez C. Misoprostol 3,4, or 5 days after methotrexate for early abortion. *Contraception* 1997;**56**:169-174.

Carbonell 1998 M800pv *{published data only}*

* Carbonell JLL, Varela L, Velazco A, Cabezas E, Fernandez C, Sanchez C. Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1998;**57**:83-88.

Cheng 1994 PGE1&T *{published data only}*

Cheng LN, Zhou YF, Song JY, Li H, Chen JK. A randomized clinical trial in comparison of termination of early pregnancy by 16,16-dimethyl-trans PGE1 ester alone or in combination with testosterone propionate. *Sheng zhi yu bi yun (Reproduction and Contraception)* 1994;**1**:29-33.

Coyaji 2007 *{published data only}*

Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one?. *BJOG* 2007;**114**:271–278.

Creinin 1994 M800&MT *{published data only}*

Creinin DM, Vittinghoff E. Methotrexate and misoprostol vs misoprostol alone for early abortion. *JAMA* 1994;**272**(15):1190-1195.

Creinin 1995 M800pv *{published data only}*

* Creinin MD, Vittinghoff E, Galbraith S, Klaisle C. A randomized trial comparing misoprostol three and seven days after methotrexate for early abortion. *American Journal of Obstetrics and Gynecology* 1995;**173**:1578-1584.

Creinin 1996 M800pv *{published data only}*

* Creinin MD. Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1996;**54**:15-18.

Creinin 1997 M800pv *{published data only}*

* Creinin MD, Krohn MA. Methotrexate pharmacokinetics and effects in women receiving methotrexate 50 mg and 60 mg per square meter for early abortion. *American Journal of Obstetrics and Gynecology* 1997;**177**:1444-1449.

Creinin 2001 *{published data only}*

* Creinin MD, Pymar HC, Schwartz JL. Mifepristone 100 mg in abortion regimens. *Obstetrics and Gynecology* 2001;**98**(3):434-439.

Creinin 2001 MI600 M400 *{published data only}*

* Creinin MD, Schwartz JL, Pymar HC, Fink W. Efficacy of mifepristone followed on the same day by misoprostol for early termination of pregnancy: report of a randomised trial. *British Journal of Obstetrics and Gynaecology* 2001;**108**:469-473.

Creinin 2004 *{published data only}*

Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. *Obstetrics and Gynecology* 2004;**103**:851-859.

Creinin 2007 *{published data only}*

Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA. Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion. *Obstetrics and Gynecology* 2007;**109**:885-894.

El-Refaey 1994 *{published data only}*

* El-Refaey H, Templeton A. Early abortion induction by a combination of mifepristone and oral misoprostol: a comparison between two dose regimens of misoprostol and their effect on blood pressure. *British Journal of Obstetrics and Gynaecology* 1994;**101**:792-796.

El-Refaey 1995 M800MI600 *{published data only}*

* El-Refaey H, Rajasekar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. *New England Journal of Medicine* 1995;**332**:983-987.

Guest 2007 *{published data only}*

Guest J, Chien PFW, Thomson MAR, Kosseim ML. Randomised controlled trial comparing the efficacy of same-day administration ofmifepristone and misoprostol for termination of pregnancy with the standard 36 to48 hour protocol. *BJOG An International Journal of Obstetrics and Gynaecology* 2007;**114**:207-215.

Hamoda 2005 *{published data only}*

Hamoda H, Ashok PW, Flett GMM, Templeton A. A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation. *BJOG: an International Journal of Obstetrics and Gynaecology* 2005;**112**:1102–1108.

Honkanen 2004 *{published data only}*

Honkanen H, Piaggio G, Von Hertzen H, Bartfai G, Erdenetungalag R, Gemzell-Danielsson K, Gopalan S, Horga M, Jerve F, Mittal S, Thi Nhu Ngoc N, Peregoudov A, Prasad R, Pretnar-Darovec A, Shah R, Song S, Tang O, Wu S. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion.II: Side effects and women's perceptions. *BJOG: an International Journal of Obstetrics and Gynaecology* 2004;**111**:715-725.

Jain 2002 M800&MI *{published data only}*

Jain JK, Dutton C, Harwood B, Meckstroth KR, Mishell DR. A prospective randomized, double-blinded, placebo-controlled trial comparing mifepristone and vaginal misoprostol to vaginal misoprostol alone for elective termination of early pegnancy. *Human Reproduction* 2002;**17**(6):1477-1482.

Jain 1999 M800&TM *{published data only}*

* Jain JK, Meckstroth KR, Park M, Mishell DR Jr. A comparison of tamoxifen and misoprostol to misoprostol alone for early pregnancy termination. *Contraception* 1999;**60**(6):353-356.

Koopersmith 1996 *{published data only}*

* Koopersmith TB, Mishell DR. The use of misoprostol for termination of early pregnancy. *Contraception* 1996;**53**:237-242.

Liao 2004 *{published data only}*

Liao A, Han XJ, Wu SY, Xiao DZ, Xiong CL, Wu XR. Randomized, double-blind, controlled trial of mifepristone incapsule versus tablet form followed by misoprostol for early medical abortion. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2004;**116**:211-216.

McKinley 1993 M600po *{published data only}*

* McKinley C, Thong KJ, Baird DT. The effect of dose of mifepristone and gestation on the efficacy of medical abortion with mifepristone and misoprostol. *Human Reproduction* 1993;**8**(9):1502-1505.

Middleton 2005 *{published data only}*

Middleton T, Schaff E, . Fielding SL, Scahill M, Shannon C, Westheimer E, Wilkinson T, Winikoff B. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. *Contraception* 2005;**72**:328-332.

Ozeren 1999 MP800&MT *{published data only}*

* Ozeren M, Bilekli C, Aydemir V, Bozkaya H. Methotrexate and misoprostol used alone or in combination for early abortion. *Contraception* 1999;**59**:389-394.

Raghavan 2009 *{published data only}*

Raghavana S, Comendant R, Digol I, Ungureanu S, Friptu V, Bracken H, Winikoff B. Two-pill regimens of misoprostol after mifepristone medical abortion through 63 days' gestational age: a randomized controlled trial of sublingual and oral misoprostol. *Contraception* 2009;**79**:84-90.

Rodger 1989 MI600 *{published data only}*

* Rodger MW, Logan AF, Baird DT. Induction of early abortion with mifepristone (RU 486) and two different doses of prostaglandin pessary (gemeprost). *Contraception* 1989;**39**(5):497-502.

Sandstrom 1999 MI600GP1pv *{published data only}*

Sandstrom O, Brooks L, Schantz A, Grinsted J, Grinsted L, Jacobsen JD, Nielsen SP. Interruption of early pregnancy with mifepristone in combination with gemeprost. *Acta Obstet Gynecol Scand* 1999;**78**:806-809.

Sang 1994 M600poPGF2pv *{published data only}*

* Sang GW, Weng LJ, Shao QX, Du MK, Wu XZ, Lu YL, Cheng LN. Termination of early pregnancy by two regimens of mifepristone with misoprostol and mifepristone with PG05 - a multicentre randomized clinical trial in China. *Contraception* 1994;**50**:501-510.

Sang 1999 M600poPGF2pv *{published data only}*

* Sang GW, He CH, Shao QX, Zhuang LQ, Weng LJ, Wu BX, Gao ES, Jiang HY, Mei QM. A large scale introductory trial on termination of early pregnancy by mifepristone in combination with different prostaglandins. *Chinese Journal for Clinical Pharmacology* 1999;**15**(5):323-329.

Schaff 2001 M800MI200 *{published data only}*

Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion. *Contraception* 2001;**64**(2):81-85.

Schaff 2000 MI200M800 *{published data only}*

Schaff EA, Fielding SL, Westhoff C, Ellertson C, Eisinger SH, Stadalius LS, Fuller L. Vaginal misoprostol administered 1,2 or 3 days after mifepristone for early medical abortion. *JAMA* 2000;**284**(15):1948-1953.

Shannon 2006 *{published data only}*

Shannon C, Wiebe E, Jacot F, Guilbert E, Dunn S, Sheldon W, Winikoff B. Regimens of misoprostol with mifepristone for early medical abortion: a randomised trial.. *BJOG* 2006;**113**:621–628.

Swahn 1989 MI200MP1po *{published data only}*

* Swahn ML, Ugocsai G, Bygdeman M, Kovacs L, Belsey EM, Van Look PFA. Effect of oral prostaglandin E2 on uterine contractility and outcome of treatment in women receiving RU 486 (mifepristone) for termination of early pregnancy. *Human Reproduction* 1989;**4**(1):21-28.

Tang 2002 *{published data only}*

Tang OS, Lee SWH, Ho PC. A prospective randomized study on the measured blood loss in medical termination of early pergnancy by three different misoprostol regimens after pretreatment with mifepristone. *Human Reproduction* 2002;**17**(11):2865-2868.

Tang 2003 *{published data only}*

Tang OS, Chan CCW, Ng EHY, Lee SWH, Ho PC. A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation. *Human Reproduction* 2003;**18**:2315-2318.

von Hertzen 2003 *{published data only}*

Von Hertzen H, Honkanen H, Piaggio G, Bartfai G, Erdenetungalag R, Gemzell-Danielsson K, Gopalan S, Horga M, Jerve F, Mittal S, Thi Nhu Ngoc N, Peregoudov A, Prasad R, Pretnar-Darovec A, Shah R, Song S, Tang O, Wu S. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I: Efficacy. *BJOG: an International Journal of Obstetrics and Gynaecology* 2003;**110**:808-818.

von Hertzen 2007 *{published data only}*

von Hertzen H, Piaggio G, Huong N, Arustamyan K, Cabezas E, Gomez M, Khomassuridze A, Shah R, Mittal S, Nair R, Erdenetungalag R, Huong T, Vy N, Phuong N, Tuyet H, Peregoudov A, on behalf of the WHO Research Group on Postovulatory Methods of Fertility Regulation. Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy:a randomised controlled equivalence trial. *Lancet* 2007;**369**:1938-1946.

von Hertzen 2009 *{published data only}*

von Hertzen H, Piaggio G, Wojdyla D, Marions L, My Huong NT, Tang OS, Fang AH, Wu SC, Kalmar L, Mittal S, Erdenetungalag R, Horga M, Pretnar-Darovec A, Kapamadzija A, Dickson K, Anh ND, Tai NV, Tuyet HTD, Peregoudov A for the WHO Research Group on Post-ovulatory Methods of FertilityRegulation. Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a randomised factorial controlled equivalence trial. *BJOG* 2009;**116**:381–389.

Wang 2000 *{published data only}*

Wang ZH. Prevent from bleeding after medical abortion through prolonged application of mifepristone with misoprostol for terminating early pregnancy. *Zhonghua Fu Chan Ke Za Zhi* 2000;**35**(9):554-557.

WHO 2000 M400po *{published data only}*

WHO Task Force on Post-ovulatory Methods of Fertility Regulation. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial. *British Journal of Obstetrics and Gynaecology* 2000;**107**:524-530.

WHO 2001 GP1pv *{published data only}*

World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation. Medical abortion at 57 to 63 days' gestation with a lower dose of mifepristone and gemeprost. *Acta Obstetrica et Gynecologica Scandinavica* 2001;**80**:447-451.

WHO 1989 *{published data only}*

* WHO Task Force on Post-Ovulatory Methods for Fertility Regulation. Termination of early human pregnancy with RU 486 (mifepristone) and the prostaglandin analogue sulprostone: a multi-centre, randomized comparison between two treatment regimens. *Human Reproduction* 1989;**4**(6):718-725.

WHO 1991 *{published data only}*

* WHO Task Force on Post-Ovulatory Methods for Fertility Regulation. Pregnancy termination with mifepristone and gemeprost: a multicenter comparison between repeated doses and a single dose of mifepristone. *Fertility and Sterility* 1991;**56**:32-40.

WHO 1993 GP1pv *{published data only}*

* WHO Task Force on Post-Ovulatory Methods of Fertility Regulation. Termination of Pregnancy with reduced doses of mifepristone. *British Medical Journal* 1993;**307**:532-537.

WHO 2001 MI200/50 *{published data only}*

WHO Task Force on Post-ovulatory Methods for Fertility Regulation. Lowering the doses of mifepristone and gemeprost for early abortion: a randomised controlled trial. *British Journal of Obstetrics and Gynaecology* 2001;**108**:738-742.

Wiebe 1999 *{published data only}*

Wiebe ER. Tamoxifen compared to methotrexate when used with misoprostol for abortion. *Contraception* 1999;**59**:265-270.

Wiebe 1999 A *{published data only}*

Wiebe ER. Tamoxifen compared to methotrexate when used with misoprostol for abortion. *Contraception* 1999;**59**:265-270.

Wiebe 1999 B *{published data only}*

Wiebe ER. Oral methotrexate compared with injected methotrexate when used with misoprostol for abortion. *Am J Obstet Gynecol* 1999;**181**:149-152.

Wiebe 2004 *{published data only}*

Wiebe ER, Trouton K. Comparing vaginal and buccal misoprostol when used after methotrexate for early abortion. *Contraception* 2004;**70**:463-466.

Wiebe 2006 *{published data only}*

Wiebe ER, Trouton KJ, Lima R. Misoprostol alone vs. methotrexate followed by misoprostol for early abortion. *International Journal of Gynecology and Obstetrics* 2006;**95**:286-287.

Winikoff 2008 *{published data only}*

Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol inmifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008;**112**(6):1303-1310.

Wu 1993 *{published data only}*

Wu YM, Li Y, Fan HM, Zhu XJ, Zheng S, Wang S, Liu B, Yan J, Lin H, Fang J. Clinical study of mifepristone in combination with tamoxifen and 15-methyl-PGF2alpha methylester for termination of early pregnancy. Sheng Zhi Yi Xue Za Zhi (Journal of reproductive medicine). 1993; Vol. 4:224-227.

Zheng 1989 MI600PGF2pv *{published data only}*

* Zheng SR. RU486 (mifepristone): clinical trials in China. *Acta Obstet Gynecol Scand Suppl* 1989;**149**:19-23.

References to studies excluded from this review

Ashok 2002 *{published data only}*

* Ashok PW, Templeton A, Wagaarchchi PT, Flett GM. Factors affecting the outcome of early medical abortion: a review of 4132 consecutive cases. *BJOG* 2002;**109**(11):1281-1289.

Aubeny 2000 *{published data only}*

* Aubeny E, Chatellier G. A randomized comparison of mifepristone and self-administered oral or vaginal misoprostol for early abortion. *European Journal of Contraception and Reproductive Health Care* 2000;**5**(3):171-176.

Cheng 1999 *{published data only}*

* Cheng L. Termination of 10-16 weeks' gestation with mifepristone plus misoprostol: a multicentre randomized clinical trial. *Zhonghua Fu Chan Ke Za Zhi* 1999;**34**(5):268-271.

Creinin 1996 A *{published data only}*

* Creinin MD, Burke AE. Methotrexate and misoprostol for early abortion: a multicenter trial. Acceptability. *Contraception* 1996;**54**:19-22.

Davis 1999 *{published data only}*

Davis AR, Miller L, Tamimi H, Gown A. Methotrexate compared with mercaptopurine for early induced abortion. *Obstetrics & Gynecology* 1999;**93**:904-909.

De Nonno 2000 *{published data only}*

* De Nonno LS, Westhoff C, Fielding S, Schaff E. Timing of pain and bleeding after mifepristone induced abortion. *Contraception* 2000;**62**(6):305-309.

ICMR 2000 *{published data only}*

Indian Council of Medical Research Task Force. A multicentre randomized comparative clinical trial of 200 mg RU486 (mifepristone) single dose followed by either 5 mg 9-methylene PGE2 Gel (meteneprost) or 600 mcg oral PGE1 (misoprostol) for termination of early pregnancy within 28 days of missed menstrual period. *Contraception* 2000;**62**:125-130.

Jacobson 1990 *{published data only}*

* Jacobson J, Bergquist C, Rydnert J, Bokstroem H, Huovinen K. No abortion-inducing effect of the ulcer-healing dose of the synthetic prostaglandin E2 analogue enprostil in first trimester. *Acta Obstetrica Gynecologica Scandinavia* 1990;**69**:135-138.

Martin 1998 *{published data only}*

* Martin CW, Brown AH, Baird DT. A pilot study of the effect of methotrexate or combined oral contraceptive on bleeding patterns after induction of abortion with mifepristone and a prostaglandin pessary. *Contraception* 1998;**58**(2):99-103.

Ngai 2000 *{published data only}*

* Ngai SW, Tang OS, Chan YM, Ho PC. Vaginal misoprostol alone for medical abortion up to 9 weeks of gestation: efficacy and acceptability. *Human Reproduction* 2000;**15**(5):1159-1162.

Norman 1992 *{published data only}*

* Norman JE, Thong KJ, Rodger MW, Baird DT. Medical abortion in women of <56 days amenorrhoea: a comparison between gemeprost (a PGE1 analogue) alone and mifepristone and gemeprost. *British Journal of Obstetrics and Gynaecology* 1992;**99**:601-606.

Swahn 1994 *{published data only}*

* Swahn ML, Kovacs L, Cekan SZ, Aedo AR, Westlund P. Termination of early pregnancy with ZK 98,734: pharmacokinetic behaviour and clinical effect. *Human Reproduction* 1994;**9**(1):57-63.

Tang 1999 *{published data only}*

* Tang OS, Gao PP, Cheng L, Lee SW, Ho PC. A randomized double-blind placebo-controlled study to assess the effect of oral contraceptive pills on the outcome of medical abortion with mifepristone and misoprostol. *Human Reproduction* 1999;**14**(3):722-725.

Wiebe 2001 *{published data only}*

* Wiebe ER. Misoprostol administration in medical abortion. A comparison of 3 regimens. *Journal of Reproductive Medicine* 2001;**46**(2):125-129.

Additional references

Bachelot 1992

Bachelot A, Cludy L, Spira A. Conditions for chosing between drug-induced and surgical abortions. *Contraception* 1992;**45**:547-559.

Beaulieu 1997

Beaulieu EE. RU 486 (Mifepristone) - A short overview of its mechanisms of action and clinical uses at the end of 1996. Annals New York Academy of Sciences. New York Academy of Sciences, 1997:47-58.

Blanchard 1999

Blanchard K, Winikoff B, Ellertson C. Misoprostol used alone for the termination of early pregnancy. *Contraception* 1999;**59**:209-217.

Bugalho 1996

Bugalho A, Faundes A, Jamisse L, Usfa M, Maria E, Bique C. Evaluation of the effectiveness of vaginal misoprostol to induce first trimester abortion. *Contraception* 1996;**53**:243-246.

Bygdeman 1985

Bygdeman M, Swahn ML. Progesterone receptor blockage. Effect on uterine contractility and early pregnancy. *Contraception* 1985;**32**:45-51.

Bygdeman 2002

Bygdeman M, Danielsson KG. Options for early therapeutic abortion. *Drugs* 2002;**62**(17):2459-2470.

Carbonell 1997b

Carbonell JLL, Varela L, Velazco A, Fernandez C. The use of misoprostol for termination of early pregnancy. *Contraception* 1997;**55**:165-168.

Costa 1998

Costa SH. Commercial availability od misoprostol and induced abortion in Brazil. *International Journal of Gynaecology and Obstetrics* 1998;**63 (suppl 1)**:S:131-139.

Creinin 1993

Creinin MD, Darney PD. Methotrexate and misoprostol for early abortion. *Contraception* 1993;**48**:339-348.

Creinin 1996b

Creinin MD, Burke AE. Methotrexate and misoprostol for early abortion: a multicenter trial. Acceptability. *Contraception* 1996;**54**:19-22.

Grimes 1997

Grimes DA. Medical abortion in early pregnancy: a review of the evidence. *Obstetrics Gynecology* 1997;**89**:790-796.

Henshaw 1994

Henshaw RC, Naji SA, Russell IT, Templeton AA. A comparison of medical abortion (using mifepristone and gemeprost) with surgical vacuum aspiration: efficacy and early medical sequelae. *Human Reproduction* 1994;**9**(11):2167-2172.

Honkanen 2002

Honkanen H, von Hertzen H. Users' perspectives on medical abortion in Finland. *Contraception* 2002;**65**(6):419-23.

Say 2002, updated 2010

Say L, Brahmi D, Kulier R, Campana A, Gulmezoglu AM. Medical versus surgical methods for first trimester termination of pregnancy. *Cochrane Database of Systematic Reviews* 2002, Issue 4. [DOI: 10.1002/14651858.CD003037.pub2.]

Sedgh 2007

Sedgh G, Henshaw SK, Singh S, Bankole A, Drescher J. Legal abortion worldwide: incidence and recent trends. *Int Fam Plan Perspect* 2007;**33**(3):106-16.

United 1990

United Kingdom Multicentre Trial. The efficacy and tolerance of mifepristone and prostaglandin in first trimester termination of pregnancy. *Br J Obstet Gynaecol* 1990;**97**:480.

Urquhart 1997

Urquhart DR, Templeton AA, Shinewi F, Chapman M, Hawkins K, McGarry J. The efficacy and tolerance of mifepristone and prostaglandin in termination of pregnancy of less than 63 days gestation: UK Multicentre Study - final results. *Contraception* 1997;**55**:1-5.

WHO 1997

WHO Scientific Group. WHO Technical Report Series. WHO. Vol. **871**, Geneva: WHO, 1997.

Winikoff 1997

Winikoff B, Irving S, Coyaji K, Caberas E, Bilian X, Sujuan G, Ming- Kun D, Krishna U, Eschen A, Ellertson C. Safety, efficacy and acceptability of medical abortion in China, Cuba and India: a comparative trial of mifepristone - misoprostol versus surgical abortion. *American Journal of Obstetrics and Gynecology* 1997;**176**:431-437.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Arvidsson 2005

Methods	computer randomisation
Participants	100 women randomised; age and gestational ages averages not given; included gestational age up to 49 days confirmed by ultrasound; exclusion criteria: contraindications for medical abortion.Setting: Karolinska Hospital, Sweden
Interventions	mifepristone 600mg (all) followed 36-48 hrs later by: group1) misoprostol 400mcg oral group 2) misoprostol 800mcg vaginal
Outcomes	experience of pain, occurrence of side-effects, duration of bleeding

Arvidsson 2005 *(Continued)*

Notes	10 women could not be reached by phone 3-7 weeks after abortion; 30 women did not agree or weren't asked to be called during this time frame

Baird 1995 GP0.5 M600po

Methods	computer generated random numbers for the first 300 women, envelopes were shuffled in batches of 20 and numbered consecutively for the reminders no blinding for clinical staff
Participants	800 pregnant women </= 63 days of amenorrhoea in Edinburgh/Scotland
Interventions	mifepristone 200mg (all) followed by: group 1: gemeprost 0.5mg vaginal and 3 tabs placebo after 48 hours group 2: misoprostol 600mcg oral and vaginal examination after 48 hours
Outcomes	complete, incomplete and missed abortion ongoing pregnancy side effects
Notes	power calculation (80% to detect 5% difference) placebos were not identical to misoprostol 1 woman needed blood transfusion (group 2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Bartley 2001 GP0.5M800pv

Methods	computer generated random numbers
Participants	999 pregnant women, < 63 days of gestation, confirmed by ultrasound if necessary, at the Royal Infirmary Hospital, Edinburgh Inclusion criteria: aged =/> 16 years, available for follow-up within 2 weeks Exclusion criteria: ectopic pregnancy, active asthma, liver or renal disease, adrenal insufficiency, anaemia, haemolytic disease, treatment with anticoagulants, smoking > 20 cigarettes/day
Interventions	mifepristone 200mg (all) followed by: group 1: gemeprost 0.5mg/vaginal group 2: misoprostol 800mcg/vaginal
Outcomes	complete, incomplete abortion, ongoing pregnancy, duration of bleeding, side effects
Notes	single blinded 2 women required blood transfusions (1 in each group)

Risk of bias

Bias	Authors' judgement	Support for judgement

Bartley 2001 GP0.5M800pv *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Birgerson 1988

Methods	random allocation, not specified
Participants	153 women, ≤ 49 days of amenorrhoea, confirmed by positive pregnancy test and pelvic examination, Uppsala, Sweden
Interventions	group 1: mifepristone 10mg / twice daily for 7 days group 2: mifepristone 25mg / twice daily for 7 days group 3: mifepristone 50mg / twice daily for 7 days (group 1 vs group 3)
Outcomes	complete, incomplete abortion ongoing pregnancy bleeding pattern side effects
Notes	no mentioning of major complications

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Blanchard 2005

Methods	random numbers generated in SPSS; numbered opaque envelopes
Participants	>18 years old in good general health and willing to return for follow-up and living <1 hr from clinic; ≤ 56 days of gestation, exclusion: less than 18 years old, suspected ectopic pregnancy. Study conducted in India and Vietnam
Interventions	misoprostol only: g1) 4X400mcg/3h/oral; g2) 2X800mcg/oral; g3) 1X600mcg/vaginal; g4) 2X800mcg/3h/oral; g5) 1X800mcg/vaginal
Outcomes	complete/incomplete abortion, ongoing pregnancy
Notes	Initially, women were randomised between the first three regimens. Subsequent review of their low efficacy resulted changing the regimens, and from that point on, women were randomized to treatment group 4 or 5.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Blanchard 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Cameron 1986 MI600GP1pv

Methods	random allocation, not specified
Participants	45 pregnant women < 56 days amenorrhoea, confirmed by pregnancy test, pelvic examination and ultrasound Exclusion criteria: multiple pregnancy, spontaneous abortion, cardiovascular or pulmonary disease, allergy, epilepsy
Interventions	group 1: mifepristone 150mg / daily for 4 days group 2: mifepristone 150mg and gemeprost 1-2 mg vaginal after 48 hours
Outcomes	complete abortion, treatment failure, complications, side effects, pain, bleeding pattern
Notes	5 women receiving gemeprost 2 mg were excluded from the analysis 1 woman received blood transfusion (group 1); 1 woman had emergency evacuation due to heavy bleeding (group 1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Carbonell 1997 M800pv

Methods	computer randomisation; sealed, opaque envelopes were numbered by a by a person unrelated to the study
Participants	300 pregnant women, ≤ 63 days of amenorrhoea confirmed by ultrasound Exclusion criteria: previous use of vitamins/folates, white blood cell count <3000/uL, platelet count <100 000/uL, haemoglobin <10.0 mg/dL, aspartate aminotransferase >2 times normal or active liver disease, serum creatinine >1.5 mg/dL or active renal disease, inflammatory bowel disease, intolerance to the medication
Interventions	methotrexate 50mg/m2 intramuscular on recruitment day and misoprostol800 mcg vaginal (self administered) on: group 1: day 3 group 2: day 4 group 3: day 5 additional 800mcg misoprostol in 48 hours interval (up to 4 doses)
Outcomes	complete, incomplete abortion (complete expulsion with additional doses of misoprostol), treatment failure, bleeding pattern, blood parameters, side effects
Notes	power calculation (85% power, significance level of 0.05) no major complications occurred

Risk of bias

Carbonell 1997 M800pv *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Carbonell 1998 M800pv

Methods	computer randomisation; sealed, opaque envelopes were numbered by a by a person unrelated to the study
Participants	315 pregnant women, ≤ 63 days of amenorrhoea confirmed by ultrasound Exclusion criteria: previous use of vitamins/folates, white blood cell count <3000/uL, platelet count <100 000/uL, haemoglobin <10.0 mg/dL, aspartate aminotransferase >2 times normal or active liver disease, serum creatinine >1.5 mg/dL or active renal disease, inflammatory bowel disease, intolerance to the medication
Interventions	methotrexate 50mg oral on recruitment day and misoprostol 800mcg vaginal (self administered) on: group 1: day 3 group 2: day 4 group 3: day 5 additional 800mcg misoprostol in 48 hours interval (up to 4 doses)
Outcomes	complete, incomplete abortion (complete expulsion with additional doses of misoprostol), treatment failure, bleeding pattern, blood parameters, side effects
Notes	power calculation (80% power, significance level of 0.05) no major complications occurred

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Cheng 1994 PGE1&T

Methods	double blind, randomisation generated centrally; sealed, opaque envelopes
Participants	151 women, ≤ 49 days of amenorrhoea confirmed by ultrasound at Shanghai Medical University without medical disorders, contraindication for the study medication or IUD in situ
Interventions	group 1: day 1-3: testosterone propionate 100mg/imi/day day 4: PGE1 ester (ONO 802) 1mg/pv/6 hourly for a maximum of 4 doses group2: day 1-3: placebo injections day 4: PGE1 ester (ONO 802) 1mg/pv/6 hourly for a maximum of 4 doses
Outcomes	complete, incomplete abortion, ongoing pregnancy, blood transfusion, duration of bleeding
Notes	no major complications were reported

Cheng 1994 PGE1&T *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Coyaji 2007

Methods	computer generated random sequence; consecutive numbered opaque envelopes
Participants	18 years or older; 300 women randomised; gestational age less than 8 weeks; study conducted between january 2004 - june 2005; no contraindications to study medication lived or worked within 1 hour of the study site, agreed to provide an address and telephone number and return for a follow-up visit study site: India (Pune and Mumbai)
Interventions	mifepristone 200mg followed after 48 hours by: group 1) 400mcg oral misoprostol and placebo 3h later group 2) 400mg misoprostol repeated once 3 hours later
Outcomes	complete abortion, side effcets
Notes	ITT done

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Creinin 1994 M800&MT

Methods	randomisation according to computer-generated random number table numbered sealed, opaque envelopes
Participants	63 pregnant women, ≤ 56 days of amenorrhoea, confirmed by ultrasound, San Francisco General Hospital Exclusion criteria: Exclusion criteria: previous use of vitamins/folates, hematocrit ≤ 0.30, white blood cell count <3000/uL, platelet count <100 000/uL, haemoglobin <10.0 mg/dL, aspartate aminotransferase >2 times normal or active liver disease, serum creatinine >1.5 mg/dL or active renal disease, inflammatory bowel disease, asthma, intolerance to the medication
Interventions	group 1: methotrexate 50mg/m2 intramuscular and misoprostol 800mcg/vaginal after 3 days group 2: misoprostol 800mcg/vaginal
Outcomes	complete abortion, duration of vaginal bleeding, side effects, change in beta-HCG levels

Creinin 1994 M800&MT *(Continued)*

Notes	power calculation (80% power, significance level of 0.05) based on 95% success with methotrexate and 75% success with misoprostol alone. The required sample size was 98. no mentioning of major complications

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Creinin 1995 M800pv

Methods	randomisation according to computer-generated random number table numbered sealed, opaque envelopes no blinding
Participants	86 pregnant women, ≤ 56 days of amenorrhoea, confirmed by ultrasound, San Francisco General Hospital Exclusion criteria: previous use of vitamins/folates, hematocrit ≤ 0.30, white blood cell count <3000/uL, platelet count <100 000/uL, haemoglobin <10.0 mg/dL, aspartate aminotransferase >2 times normal or active liver disease, serum creatinine >1.5 mg/dL or active renal disease, inflammatory bowel disease, asthma, intolerance to the medication
Interventions	methotrexate 50mg/m2 intramuscular followed by: group 1: misoprostol 800mcg/vaginal after 3 days group 2: misoprostol 800mcg/vaginal after 7 days
Outcomes	complete abortion, duration of vaginal bleeding, side effects, change in beta-HCG levels
Notes	power calculation (80% power, significance level of 0.05) no major complications occurred

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Creinin 1996 M800pv

Methods	randomisation according to random number tables sealed, opaque envelopes were numbered by a by a person unrelated to the study no blinding
Participants	20 pregnant women, ≤49 days, confirmed by ultrasound, Magee-Women's Hospital, Pennsylvania, USA Exclusion criteria: previous use of vitamins/folates, haemoglobin <10.0 mg/dL, aspartate aminotransferase >2 times normal or active liver disease, serum creatinine >1.5 mg/dL or active renal disease, inflammatory bowel disease, intolerance to the medication
Interventions	group 1: methotrexate 25mg/orally followed by misoprostol 800mcg/vaginal after 7 days group 2: methotrexate 50mg/orally followed by misoprostol 800mcg/vaginal after 7 days

Creinin 1996 M800pv *(Continued)*

Outcomes	complete abortion, duration of vaginal bleeding, side effects, change in haemoglobin/aspartate transferase
Notes	no major complications occurred

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Creinin 1997 M800pv

Methods	randomisation according to computer-generated random number table numbered sealed, opaque envelopes prepared by a person unrelated to the study no blinding
Participants	20 pregnant women, ≤49 days, confirmed by ultrasound, Magee-Women's Hospital, Pennsylvania, USA Exclusion criteria: previous use of vitamins/folates, hematocrit < 37%, white blood cell count <3000/uL, platelet count <100 000/uL, haemoglobin <10.0 mg/dL, aspartate aminotransferase >2 times normal or active liver disease, serum creatinine >1.5 mg/dL or active renal disease, inflammatory bowel disease, asthma, intolerance to the medication
Interventions	group 1: methotrexate 50mg/m2 followed by misoprostol 800mcg/vaginal after 7 days group 2: methotrexate 60mg/m2 followed by misoprostol 800mcg/vaginal after 7 days
Outcomes	complete abortion, time to passing of conceptus, side effects, methotrexate levels,change in haemoglobin/aspartate transferase
Notes	no blinding no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Creinin 2001

Methods	random number tables in blocs of ten, sealed opaque envelopes prepared by person not involved in the trial
Participants	80 pregnant women, ≤ 49 days pregnant, single pregnancy, confirmed by ultrasound, at the University hospital Pittsburgh, USA; exclusion criteria: contraindication to mifepristone/misoprostol administration, haemoglobin < 10 gm/dL, cardiovascular disease, coagulopathies, IUCD in situ, breast feeding
Interventions	mifepristone 100mg (all) after 2 days, home administration:

Creinin 2001 *(Continued)*

	group 1: misoprostol 400mcg oral group 2: misoprostol 800mcg vaginal
Outcomes	complete abortion, onset of bleeding &cramping, duration of bleeding, side effects
Notes	power calculation power calculation (80% power, significance level of 0.05) no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Creinin 2001 MI600 M400

Methods	random number tables, sealed opaque envelopes
Participants	86 pregnant women, =/> 18 years, ≤ 49 days pregnant, single pregnancy, at the University hospital Pittsburgh, USA exclusion criteria: contraindication to mifepristone/misoprostol administration, haemoglobin < 10 gm/dL, cardiovascular disease, coagulopathies, IUCD in situ, breastfeeding
Interventions	mifepristone 600mg (all) group 1: misoprostol 400mcg after 6-8 hours/oral group 2: misoprostol 400mcg after 48 hours/oral
Outcomes	complete abortion, onset and duration of bleeding, side effects
Notes	no blinding no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Creinin 2004

Methods	computer generated randomisation, permuted blocs, stratified by centre; sequentially numbered opaque envelopes
Participants	26 years old; 1080 women randomized no more than 63 days gestation confirmed by ultrasound; average gestational age of 51 days; willing to have surgical procedure and had a telephone; conducted in 2002-2003 in USA MAgee-Women's Hospital in Pittsburgh, Pennsylvania, columbia University, NY, Boston University,Massachusetts University of Rochester, NY
Interventions	mifepristone 200mg followed by misoprostol 800mcg vaginal: group1: administered 6-8 hours after mifepristone

Creinin 2004 *(Continued)*

	group 2: administered 23-25 hours after mifepristone
Outcomes	Complete abortion, side-effects, bleeding, acceptability
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Creinin 2007

Methods	computer generated random numbers, randomisation centrally, permuted block design with varying block sizes; randomisation after taking mifepristone ; no blinding; opaque envelopes
Participants	1128 women enrolled;mean age 27 years, women with no more than 63 days gestation (mean gestational age 51-52 days gestation) and willing to follow-up and with access to a telephone. Exclusion criteria: contraindications to mifepristone or misoprostol, Hbg< 10, IUD in place, on anticoagulants or with coagulopathy, active cervicits or currently breastfeeding. Gestational age confirmed by US. 4 academic centers in the USA; University of Pittsburgh, Oregon Health and Science University, Northwestern University, University of Southern California
Interventions	mifepristone 200mg followed by: group 1: within 15 minutes, 800mcg misoprostol vaginal group 2: 23-25 hours later, 800mcg misoprostol vaginal
Outcomes	complete abortion; side-effect; bleeding; acceptibility
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

El-Refaey 1994

Methods	sealed, opaque envelopes random assignment before misoprostol administration
Participants	150 pregnant women </= 56 days of amenorrhoea, confirmed by ultrasound
Interventions	group 1: mifepristone 200mg and misoprostol 800mcg/oral after 48 hours group 2: mifepristone 200mg and misoprostol 400mcg after 48 hours plus 400mcg 2 hours later/oral
Outcomes	changes in blood pressure, pulse rate and temperature

El-Refaey 1994 *(Continued)*

	complete and incomplete abortion ongoing pregnancy side effects bleeding pattern
Notes	power calculation (5% significance level to detect a 20% reduction in incidence of side effects) no mentioning of major complications

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

El-Refaey 1995 M800MI600

Methods	computer generated random assignment before misoprostol administration, sealed opaque envelopes
Participants	270 women ≤ 63 days of amenorrhoea, confirmed by ultrasound Exclusion criteria: contraindication for the use of mifepristone and/or misoprostol
Interventions	group 1: mifepristone 600mg and misoprostol 800mcg/orally after 48 hours group 2: mifepristone 600mg and misoprostol 800mcg/vaginally (self-administration) after 48 hours
Outcomes	complete, incomplete and missed abortion ongoing pregnancy expulsion within 4 hours expulsion without need for surgery side effects
Notes	power calculation (5% significance level to detect difference of 10% in the incidence of women aborting within 4 hours vaginal misoprostol by self administration 1 woman received a blood transfusion (group 2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Guest 2007

Methods	computer generated fixed blocks of 20; 1:1 randomisation; sealed opaque envelopes
Participants	450 women aged 24-26 years; no more than 63 days gestation confirmed by US (average 51 days of gestation); exclusion criteria: contraindications for study medication, breastfeeding, Hbg<10, coagulopathy or treatment with anticoagulants, IUD in situ, presence of cardiovascular disease, ectopic pregnancy; study conducted between September 2003 - March 2005
Interventions	mifepristone 200mg followed by: group 1: 800mcg vaginal misoprostol after 6 hours

Guest 2007 *(Continued)*

	group 2: 800mcg of vaginal misoprostol after 36-48 hrs later
Outcomes	complete abortion, side effcets, acceptability
Notes	ITT analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Hamoda 2005

Methods	random number tables; sealed opaque envelopes
Participants	340 women, average age 24 years randomised; average gestational age 65-68 days. Exclusion criteria: <16 years, severe asthma,haemorrhagic disorders and treatment with anticoagulants, known allergy to prostaglandins, history of cardiac disease, smoking over the age of 35 years with ECG abnormalities, breastfeeding. study conducted at Aberdeen Royal Infermary, UK, from July 2002 - October 2003
Interventions	mifepristone 200 mg, followed 36-48 hours after by: group 1: 600mcg sublingual misoprostol, followed 3 hours later by 400mcg (if 9-13 weeks gestation, a third dose of 400mcg was administered) group 2: 800mcg vaginal misoprostol, followed 3 hours later by 400mcg (if 9-13 weeks gestation, a third dose of 400mcg was administered)
Outcomes	complete/incomplete abortion, missed abortion, continuing pregnancy
Notes	No ITT; LTFU identical (13) in each group (total 26)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - adequate

Honkanen 2004

Methods	computer generated random sequence; packing company prepared bags containing the medication according to the randomisation sequence
Participants	2219 women; mean age 27 years; </= 63 days of amenorrhoea; Inclusion criteria:single intrauterine pregnancies, haemoglobin > 100 g/L . Exclusion criteria: medical contraindications or allergy for either mifepristone or misoprostol; past or present thromboembolism; liver disease, pruritus of pregnancy; previous surgery of uterine cervix; presence of an intrauterine device; suspected or proven ectopic pregnancy; smoking > 10 cigarettes/day; risk factor for cardiovascular disease; breastfeeding;

Honkanen 2004 *(Continued)*

	Study was conducted from October 1998 - Decembre 2000 in 15 cities in 11 countries, including developed and developing countries: Beijing, Hong Kong and Shanghai - China; Chandigarh, Mumbai and New Delhi - India; Helsinki - Finland; Ho Chi Minh City - Viet Nam; Ljubljana -Slovenia; Oslo - Norway; Singapore - Singapore; Stockholm - Sweden; Szeged - Hungary; Targu Mures - Romania; and Ulaanbaatar - Mongolia.
Interventions	mifepristone 200mg followed 36-48 hours later by: group 1: misoprostol 800mcg orally followed by misoprostol 400mcg twice/day for 6 days oral group 2: misoprostol 800mcg vaginally followed by misoprostol 400mcg twice/day for 6 days oral group 3: misoprostol 800mcg vaginally followed by placebo tablets twice/day for 6 days oral
Outcomes	side-effects and acceptability
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - adequate

Jain 2002 M800&MI

Methods	computer generated random table, opaque vials
Participants	250 healthy women, </=56 days of amenorrhoea, confirmed by ultrasound, Exclusion criteria: evidence of threatened spontaneous abortion, uterine infection, anaemia, bleeding disorders, cardiovascular or cerebrovascular disease, uterine leiomyomata, allergy against the study medication.
Interventions	group 1: mifepristone 200mg, misoprostol 800mcg/pv on day 3, repeated on day 4 if gestational sac present group 2: Placebo, misoprostol 800mcg/pv on day 3, repeated on day 4 if gestational sac present
Outcomes	successful abortion, side effects
Notes	Placebos were vitamin C tablets (not identical); opaque vials were used to blind the investigator power calculation (5% significance level to detect a 5% difference in success rates between the 2 study groups) no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Jain 1999 M800&TM

Methods	randomisation by using random number tables
Participants	150 women pregnant ≤ 56 days confirmed by ultrasound exclusion criteria: cervical dilatation, anaemia, pelvic inflammatory disease, uterine bleeding, uterine leiomyomata, serious medical problems, allergy or contraindications to the study medication
Interventions	group 1: tamoxifen 20mg/twice daily and misoprostol 800mcg/pv after 48 hours group 2: placebo twice daily and misoprostol 800mcg/pv after 48 hours
Outcomes	complete/incomplete abortion, ongoing pregnancy, complications, side effects
Notes	treatment and placebo were placed in identical capsules no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A- Adequate

Koopersmith 1996

Methods	randomisation into 3 groups randomisation procedure not stated
Participants	58 women, pregnant ≤ 10 weeks, confirmed by ultrasound, University Hospital Los Angeles, USA Exclusion criteria: uterine infection, prior uterine bleeding, cervical dilatation, anaemia, cardiovascular or cerebral disease, allergy to misoprostol
Interventions	group A: misoprostol 100mcg/vaginally/ 8 hourly to a maximum of 6 doses group B: misoprostol 100mcg/vaginally/ 8 hourly to a maximum of 6 doses and tamoxifen 10mg/orally after the first dose of misoprostol group C: misoprostol 100mcg/vaginally/ 8 hourly to a maximum of 6 doses and laminaria/intracervical immediately before the first dose of misoprostol the dose of misoprostol was increased after the success rate was unsatisfactory after the first 26 women
Outcomes	complete abortion, failure rate, side effects, mean number of doses of misoprostol used, time until passing of conceptus
Notes	no mentioning of major complications

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Liao 2004

Methods	computer random table; use of identical appearing packages and capsules/ tablets from pharmacy; identical placebo tablets
Participants	480 women,average age 26 years; </= 49 days gestation confirmed by ultrsound; Exclusion criteria: abnormal menses, IUD in situ, contraindications for use of study medication; study conducted between November 2001 to June 2002 in 3 hospitals affiliated to University of Beijing, China
Interventions	group 1: mifepristone: 50mg, then 12 hrs later 25mg, then 12 hrs later 50mg, and finally, 12 hrs later, 25mg (total: 150mg). 24 hrs after last dose 600mcg misoprostol orally group 2: mifepristone 30mg, then 15mg every 12 hours for 3 doses (total: 75mg). 24 hrs after last dose, 600mcg misoprostol orally.
Outcomes	complete abortion
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - adequate

McKinley 1993 M600po

Methods	identical envelopes, shuffled and numbered consecutively
Participants	220 pregnant women, ≤ 63 days of amenorrhoea, University hospital Edinburgh, Scotland
Interventions	group 1: mifepristone 200mg and misoprostol 600mcg/orally after 48 hours group 2: mifepristone 600mg and misoprostol 600mcg/orally after 48 hours
Outcomes	complete and incomplete abortion, time until passing of conceptus, side effects, bleeding pattern, analgesia use
Notes	blinding for outcome assessment no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Middleton 2005

Methods	computer generated randomisation in blocs of 8; sealed envelopes
Participants	442 women < 56 days randomised;mean age 26 years; mean gestaional age 47 days; study conducted between December 2001- June 2004 at two clinics at University of Rochester; USA

Middleton 2005 *(Continued)*

Interventions	1-2 days after mifepristone 200mg: group 1: misoprostol 800mcg buccal group 2: misoprostol 800mcg vaginal buccal: 2 tablets placed inside each cheek and remainders swallowed after 30 minutes; vaginal: all 4 tablets placed profond into the vagina with 1 finger
Outcomes	complete abortion, side effects, acceptability
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B-unclear

Ozeren 1999 MP800&MT

Methods	random number tables; sealed opaque envelopes, sequentially numbered
Participants	108 women ≤ 63 days of amenorrhoea confirmed by ultrasound, University hospital Trabzon, Turkey exclusion criteria: haemoglobin < 100 g/L, leucocytaemie, active liver disease, active renal disease, inflammatory bowel disease, history of methotrexate/ misoprostol intolerance
Interventions	group 1. methotrexate 50mg/m2/imi group 2: misoprostol 800mcg/pv group 3: methotrexate 50mg/m2/imi and misoprostol 800mcg/pv after 3 days
Outcomes	complete abortions, ongoing pregnancies, side effects
Notes	no major complications were reported; 10/36 women in the misoprostol only group received additional misoprostol on day 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Raghavan 2009

Methods	random code generated in blocs of 10; sequentially numbered, sealed envelopes
Participants	480 women; </= 63 days gestation. gestational age confirmed by ultrasound if needed; exclusion criteri-a:ectopic pregnancy, contraindications to study medication, treatment with anticoagulants, lived more than 1 hour away from hospital; study conducted between July 2005 to November 2006 atUniversity hospital Chisinau, Moldova

Raghavan 2009 *(Continued)*

Interventions	mifepristone 200mg followed 24 hrs later by: group 1: misoprostol 400mcg sublingual group 2: misoprostol 400mcg oral for sublingual: tablet for 30 min under the tongue and swallow rest after; no repeat doses of misoprostol offered
Outcomes	complete abortion, side effects, acceptibility
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B-unclear

Rodger 1989 MI600

Methods	randomisation not stated
Participants	120 pregnant women, <56 days of amenorrhoea, Gynaecological Out-Patient Department, Royal Infirmary Hospital, Edinburgh, Scotland
Interventions	mifepristone 600mg (all) group 1: gemeprost 0.5mg/pv after 48 hours group 2: gemeprost 1mg/pv after 48 hours
Outcomes	complete, incomplete abortion, onset and duration of bleeding, side effects, haemoglobin levels
Notes	1 woman received blood transfusion (group 2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Sandstrom 1999 MI600GP1pv

Methods	randomly allocated; using sealed envelopes
Participants	64 pregnant women, ≤ 56 days, Hillerod Hospital, Denmark Exclusion criteria: previous uterine surgery, previous abnormal vaginal bleeding, oncomitant medication, IUD in situ, contraindication to one of teh study drugs
Interventions	all: mifepristone 600mg group1: gemeprost 1mg/pv after 24 hours

Sandstrom 1999 MI600GP1pv *(Continued)*

	group 2: gemeprost 1mg/pv after 48 hours
Outcomes	complete, incomplete abortion, side effects
Notes	1 woman needed blood transfusion, not mentioned what group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Sang 1994 M600poPGF2pv

Methods	random number tables
Participants	600 women , ≤ 49 days of pregnancy, multicentre trial in 5 hospitals in Shanghai, China; pregnancy confirmed by gynaecological examination, urine pregnancy test or ultrasound; women were included if there was no history of medical disorders, no IUCD in situ and no contraindication for the study medication
Interventions	group 1: mifepristone 150mg divided into 5 doses, orally, within 3 days; misoprostol 600mcg orally 36-48 hours later group 2: mifepristone 150mg divided into 5 doses /po, within 3 days; PGF2alpha /pv 36-48 hours later group 3: mifepristone 200mg po; misoprostol 600mcg/po after 36-48 hours
Outcomes	complete, incomplete abortion, duration of bleeding, time of resuming of menses, side effects
Notes	no mentioning of major complications

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Sang 1999 M600poPGF2pv

Methods	randomisation was generated centrally and women were randomised within centres; sealed opaque envelopes
Participants	multicentre trial, 78 hospitals and family planning clinics from 8 provinces in China; 17542 pregnant women, ≤ 49 days of amenorrhoea, pregnancy confirmed by gynaecological examination, urine pregnancy test or ultrasound; women were included if there was no history of medical disorders, no IUCD in situ and no contraindication for the study medication
Interventions	mifepristone 150mg divided into 5 doses taken orally within 3 days group 1: prostaglandin F2alpha 1mg/pv 36-48 h after first dose of mifepristone group 2: misoprostol 600mcg/po 36-48 h after first dose of mifepristone

Sang 1999 M600poPGF2pv *(Continued)*

Outcomes	complete, incomplete abortion, duration of vaginal bleeding, time to resume menses, side effects, women's satisfaction with the procedure
Notes	1 woman had an allergic shock after misoprostol (group 2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Schaff 2001 M800MI200

Methods	computer generated random assignment, open-label
Participants	multicentre trial at 15 sites in the USA, incl. hospitals, non-profit abortion facilities, private family practice and gynaecologist offices 1168 women, ≤ 63 days pregnant confirmed by ultrasound, without clinical or haematological abnormalities or contraindication to the trial medication
Interventions	all women received mifepristone 200mg on day 1 group 1: 800mcg misoprostol/po minimum 24 hours after at home group 2: misoprostol 800mcg/pv minimum 24 hours after at home
Outcomes	complete, incomplete abortion, time to bleeding, side effects
Notes	open - labelled study, power calculation to detect a 5 % difference from 95% to 90% efficacy no hospitalisations and no blood transfusions

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Schaff 2000 MI200M800

Methods	computer generated random assignment, allocation, randomisation stratified by sites, allocation was 'concealed'; 53 women used repeat dose of misoprostol - not described teh number of women per group receiveing additional misoprostol
Participants	multicentre trial (16 centres), 2295 women with pregnancies ≤ 56 days confirmed by ultrasound; from 16 US primary care and referral abortion facilities; routine inclusion and exclusion criteria
Interventions	all women received mifepristone 200mg on day 1 group 1: misoprostol 800mcg/pv next day at home group 2: misoprostol 800mcg/pv 2 days later at home group 3: misoprostol 800mcg/pv 3 days later at home
Outcomes	complete abortion, acceptability, adverse effects

Schaff 2000 MI200M800 *(Continued)*

Notes	2 women received blood transfusion (not mentioned which group)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Shannon 2006

Methods	computer generated rondom numbers in group of 15; misoprostol tablets were providede in sealed, opaque envelopes after administration of mifepristone.
Participants	971 women, mean age 28 years, < 56 days of gestation; mean gestational age of 44 days. Exclusion criteria: haemoglobin < 9.5 g/dl, active hepatic or renal disease, type I diabetes mellitus, adrenal insufficiency, glaucoma, sickle cell anaemia, coagulopathy, uncontrolled seizure disorder, severe cardiovascular disease, allergy or intolerance to study medication, use of chronic oral steroid medications or anticoagulants Study conducted in 2001 at University of British Columbia; University of Sherbrooke; Laval University; University of Toronto; Canada
Interventions	Mifepristone 200mg followed 24-28 hours later by: group 1: misoprostol 400mcg oral group 2: misoprostol 600mcg oral group 3: 800mcg misoprostol vaginal. Misoprostol self administered at home. Participants were advised to take a second dose of misoprostol in case bleeding was less than normal menstruation. Ultrasound after 7 days - if ongoing pregnancy: misoprostol 800mcg vaginally
Outcomes	complete abortion, acceptability, side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A -adequate

Swahn 1989 MI200MP1po

Methods	randomly allocated
Participants	42 pregnant women, ≤ 49 days of amenorrhoea, confirmed by ultrasound
Interventions	all: mifepristone 25mg/twice daily/ for 4 days (=200mg in total) and: group 1: 1 placebo a.m. and p.m./orally

Swahn 1989 MI200MP1po *(Continued)*

	group 2: PGE2 (minprostin) 1mg/a.m. and placebo /p.m. /orally group 3: PGE2 1mg/ a.m. and p.m. /orally
Outcomes	complete, incomplete abortion failures, complaints, hormone levels (E2 prostaglandin, beta-HCG, prolactin) bleeding pattern
Notes	originally planned sample size was 120: study was discontinued due to interim analysis which showed no difference between placebo and PGE2 in the complete abortion rate no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Tang 2002

Methods	computer generated random table
Participants	150 pregnant women , </= 63 days of amenorrhoea, confirmed by ultrasound at the University Hospital Hong Kong inclusion criteria: good health, willing to use barrier methods for contraception until first menses after termination, haemoglobin level >110g/L exclusion criteria: significant past or present illness, allergy/contraindication towards study medication, intrauterine device, heavy smoker, breast feeding
Interventions	Mifepristone 200 mg for all women group A: misoprostol 800mcg/po and misoprostol 400mcg/X2/day/po for day 4-10 group B: misoprostol 800mcg/pv on day 3 and misoprostol 400mcg/X2/day/po for day 4 -10 group C: misoprostol 800mcg/pv on day 3 and placebo tablets on day 4-10
Outcomes	complete, incomplete, missed abortion, ongoing pregnancy, blood loss, haemoglobin levels
Notes	no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Tang 2003

Methods	computer generated random numbers; double blinded: women received placebo for vaginal application in the sublingual group; and placebo tablets for sublingual application in the vaginal group

Tang 2003 *(Continued)*

Participants	224 women, average age 23 years, </= 9 weeks of gestation; average gestational age 7.7 weeks; gestational age confirmed by ultrasound; exclusion criteria: using prescription drugs regularly, IUD in situ, breatsfeeding, multiple pregnancies and heavy smoking. Study conducted at University of Hong Kong.
Interventions	mifepristone 200mg followed 48 hours later by: group1: misoprostol 800mcg sublingual group 2:misoprostol 800mcg vaginal
Outcomes	complete/incomplete abortion, ongoing pregnancy; haemoglobin concentration; days of bleeding; induction-abortion intervall, side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A-adequate

von Hertzen 2003

Methods	see Honkanen 2004
Participants	
Interventions	
Outcomes	complete, incomplete abortion
Notes	

von Hertzen 2007

Methods	centrally; random permuted blocs of 10;sealed, sequentially labeled envelopes
Participants	2066 women; average age 27 years; inclusion criteria: haemoglobin > 95g/L, gestational age </= 63 days, willing to have surgical procedure in case of failure, no serious illnesses, no contraindications for use of study medication, no uterine or cervical scars, no: uncontrolled asthma, hypertension, valvular heart disease, IUD in situ, history of thromboembolism or hemolytic disease, sickle cell anemia or liver disease. Gestational age confirmed by ultrasound. Study conducted at 11 obstetrics and gynaecologic teaching departments in 6 coutries (Armenia, Cuba, Georgia, India, Mongolia, Viet Nam)
Interventions	Misoprostol 3 doses of 800mcg each, in the manner of one of the following: group 1:sublingual every 3 h group 2: sublingual every 12 h group 3: vaginal every 3 h

von Hertzen 2007 *(Continued)*

	group 4: vaginal every 12 h
Outcomes	complete, incomplete abortion, side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - adequate

von Hertzen 2009

Methods	computer generated, central randomisation, random permutation in groups of 8, stratified by gestational age; sealed, opaque sequentially numbered envelopes
Participants	2181 women; gestational age </=63 days, inclusion criteria: haemoglobin >100g/L, willing to have surgical abortion for failure, agreed to return for follow-up. exclusion criteria: ill health, contraindications to study medication, severe uncontrolled asthma, porphyria, valvular heart disease, smoking and another risk for CV disease, glaucoma, thromboembolism, liver disease, IUD in situ, breastfeeding, haemolytic disorders. Gestational age confirmed by ultrasound. Study conducted between 2003-2005 at 13 departments of obstetrics and gynaecology in nine countries (China, Hungary, India, Mongolia, Romania, Slovenia, South Africa, Viet Nam, Serbia)
Interventions	group 1: mifepristone 100 mg and 24 h later misoprostol 800 mcg vaginal group 2: mifepristone 100 mg and 48 h later misoprostol 800 mcg vaginal group 3: mifepristone 200 mg and 24 h later misoprostol 800mcg vaginal group 4: mifepristone 200 mg and 48 h later misoprostol 800mcg vaginal follow up at 2 and 6 weeks
Outcomes	complete , incomplete, missed abortion, side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A-adequate

Wang 2000

Methods	women were randomly divided into 2 groups by 2:1 ratio
Participants	Multicentre trial in 9 hospitals in Hebei,China; 1612 pregnant women ≤ 49 days of amenorrhoea, confirmed by ultrasound; without clinical or haematological abnormalities,contraindication for the study medication or IUD in situ.

Wang 2000 *(Continued)*

Interventions	group 1: day 1: mifepristone 50 mg/po 12 hours apart (= total of 100 mg) day 2 to day 7: mifepristone 25 mg/po daily (= total of 250 mg) day 3: misoprostol 600 mcg/po day 4 to day 6: misoprostol 200 mcg daily (= total of 600 mcg) group 2: day 1: mifepristone 50 mg/po then 25 mg/12 hourly/4 times (= total of 150 mg) day 3: misoprostol 600 mcg/po
Outcomes	complete/incomplete abortion, duration of bleeding, resuming of menses, side effects
Notes	post-randomisation exclusion, protocol deviation, loss to follow-up not mentioned no mentioning of major complications

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

WHO 2000 M400po

Methods	computer generated random numbers,
Participants	multicentre trial: Beijing, Havana, Helsinki, Ho Chi Min City, Hong Kong, Ljubljana, Melbourne, Moscow, Mumbai, Shanghai, Stockholm, St Petersburg, Szeged, Tbilisi, Tianjin, Tunis, Yerevan, 1589 women ≤ 63 days of amenorrhoea, with positive pregnancy test and uterine size consistent with menstrual history exclusion criteria: contraindications for study drug use, history of thromboembolism, liver disease, regular use of prescription drugs, intrauterine device, suspected ectopic pregnancy, heavy cigarette smoking, breastfeeding, irregular menses
Interventions	group 1: mifepristone 200 mg/po group 2: mifepristone 600 mg/po both groups received misoprostol 400 mcg/po after 48 hours
Outcomes	complete/incomplete/missed/unclassified failed abortion, side effects
Notes	identical placebos, identical pill bottles; power calculation (90% power, significance level of 0.05) no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

WHO 2001 GP1pv

Methods	computer generated sequence of random numbers in block of ten,

WHO 2001 GP1pv *(Continued)*

	identical placebo tablets
Participants	multicentre trial, 10 centres: Chandigarh, Edinburgh, Havana, Hong Kong, Ljubljana, Shanghai, Stockholm, Szeged, Tbilisi, Tianjin 896 women, at 57 to 63 days of gestation with regular menstrual cycles, pregnancy confirmed clinically or by ultrasound exclusion criteria: contraindication to the study drugs, chronic respiratory, digestive, endocrine, genito-urinary, neurological or cardio-vascular disease, severe liver disease, history of thrombo-embolism, IUCD in situ, breastfeeding
Interventions	group 1: mifepristone 200 mg group 2: mifepristone 600 mg and gemeprost 1 mg after 48 hours (all)
Outcomes	complete, incomplete, missed abortion, time to onset of bleeding, duration of bleeding, time to return to menses, bleeding before gemeprost, time of expulsion
Notes	power calculation (80% power at a significant level of 0.05) intention -to -treat analysis 2 women received blood transfusion, not mentioned which group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

WHO 1989

Methods	randomly allocated 10/261 post-randomisation exclusions: 2: cycle length < 25 days 6: > 49 days pregnant 1: pregnancy not confirmed 1: wrongly randomised 1 woman was lost to follow-up (group 2)
Participants	Multicentre, Hospitals in Aberdeen, Milan, New Delhi, Shanghai, Singapore, Stockholm, Szeged 261 pregnant women, ≤ 35 years, ≤ 49 days of amenorrhoea confirmed by ultrasound and beta-HCG if US inconclusive inclusion criteria: regular cycles (25-35 days) for last 3 months exclusion criteria: unsure about dates, intrauterine device in situ, hormonal contraception during last cycle and intention to start hormonal contraception before first period after abortion
Interventions	group 1: mifepristone 25mg/twice daily for 3 days and sulprostone0.25 mg /intramuscular/ on third day a.m. group 2: mifepristone 25mg /twice daily for 4 days and sulprostone0.25 mg /intramuscular/ on fourth day a.m.
Outcomes	complete, and incomplete abortion failure (intact amniotic sac on follow-up at 2 weeks) undetermined outcome hormone levels (beta-HCG, estradiol, prolactin, cortisol, prostaglandin)

WHO 1989 *(Continued)*

Notes	2 women received blood transfusion; not mentioned which group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

WHO 1991

Methods	randomisation at WHO, using random permutation block technique with block size of 8, random numbers were provided to each centre in a sealed envelope
Participants	multicentre; 10 mostly academic hospitals: Aberdeen, Havana, Hong Kong, Ljubljana, Milan, Shanghai, Singapore, Stockholm, Szeged, Wuhan. 385 women were randomised. inclusion criteria: amenorrhoea ≤ 49 days, regular cycles (25-35 days) for last 3 months exclusion criteria: unsure about dates, intrauterine device in situ, hormonal contraception during last cycle and intention to start hormonal contraception before first period after abortion
Interventions	group 1: mifepristone 25mg/12 hourly/ 5 doses and gemeprost 1mg/vaginally 60 hours after the start of the treatment group 2: mifepristone 600mg/single dose and gemeprost 1mg/vaginally 60 hours after the start of the treatment
Outcomes	complete, incomplete, missed abortion, continuing pregnancy, side effects, bleeding pattern, haemoglobin and hormone levels
Notes	1 woman received blood transfusion; not mentioned which group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

WHO 1993 GP1pv

Methods	randomisation at WHO, using random permutation block technique with block size of 9, tablets were disposed into labelled bottles, placebos were added to women receiving the lower dose so that all received 3 tablets)
Participants	multicentre, Hospitals in Aberdeen, Edinburgh, Havana, Hong Kong, Ljubljana, Milan, Shanghai, Stockholm, Szeged, Tianjin, Wuhan 1182 pregnant women with a menstrual delay of 7-28 days inclusion criteria: regular cycles (25-35 days) for last 3 months, pregnancy confirmed by ultrasound exclusion criteria: unsure about dates, intrauterine device in situ, hormonal contraception during last cycle and intention to start hormonal contraception before first period after abortion, contraindication to mifepristone/misoprostol, regular use of prescribed drugs

WHO 1993 GP1pv *(Continued)*

Interventions	group 1: mifepristone 200mg/oral group 2: mifepristone 400mg/oral group 3: mifepristone 600mg/oral and prostaglandin 1mg/vaginally after 48 hours (all)
Outcomes	complete, incomplete, missed abortion, continuing pregnancy, side effects, haemoglobin levels, side effects
Notes	3 women received blood transfusion; not mentioned which group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

WHO 2001 MI200/50

Methods	computer generated number sequence
Participants	multicentre trial, 13 centres: Aberdeen, Chandigarh, Edinburgh, Havana, Hong Kong, Ljubljana, Lusaka, Shanghai, Singapore, Stockholm, Szeged, Tbilisi, Tianjin 1224 women <57 days pregnant inclusion criteria: regular cycles, no hormonal contraception or IUD use before first menses after abortion exclusion criteria: medical contraindication for the study medication, history of thromboembolism, liver disease, pruritus in pregnancy, IUD in situ, breastfeeding, heavy smokers
Interventions	group 1: mifepristone 50mg/po and gemeprost 0.5mg/pv on day 3 group 2: mifepristone 50mg/po and gemeprost 1.0mg/pv on day 3 group 3: mifepristone 200mg/po and gemeprost 0.5mg/pv on day 3 group 4: mifepristone 200mg/po and gemeprost 1.0mg/pv on day 3
Outcomes	complete /incomplete/missed abortion, side effects
Notes	group 1: was discontinued as interim analysis showed below cut-off results. no blinding for gemeprost 7 women received blood transfusion (2 group 1, 2 group 2, 1 group 3, 2 group4)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Wiebe 1999

Methods	computer generated list of random numbers, sealed, opaque envelopes

Wiebe 1999 *(Continued)*

Participants	398 women, ≤ 7 weeks pregnant confirmed by ultrasound, University Hospital Vancouver, Canada exclusion criteria: abnormal haematologic parameters
Interventions	Phase 1: group 1: Tamoxifen 40mg/po and 800mcg misoprostol/pv > 48 hours group 2: Methotrexate 50mg/m2 and misoprostol 800mcg/pv >96 hours Phase 2: group 1: Tamoxifen 40 mg/day for 4 days (= total dose of 160mg) and misoprostol 800mcg/pv > 48 hours group 2: Methotrexate 50 mg/m2 and misoprostol 800mcg/pv >96 hours
Outcomes	failure rate, side effects, women's preference
Notes	no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Wiebe 1999 A

Methods	see Wiebe 1999
Participants	see Wiebe 1999
Interventions	Phase 2: group 1: Tamoxifen 40 mg/day for 4 days (= total dose of 160mg) and misoprostol 800 mcg/pv > 48 hours group 2: Methotrexate 50 mg/m2 and misoprostol 800mcg/pv >96 hours
Outcomes	see Wiebe 1999
Notes	see Wiebe 1999

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Wiebe 1999 B

Methods	computer generated list of random numbers, sealed, opaque envelopes
Participants	100 women, ≤ 7 weeks pregnant confirmed by ultrasound, University Hospital Vancouver, Canada exclusion criteria: abnormal haematologic parameters, systemic disease, intolerance to study medication

Wiebe 1999 B *(Continued)*

Interventions	group 1: methotrexate 50 mg/m2/po and misoprostol 600mcg/pv > 96 hours group 2: methotrexate 50 mg/m2/imi and misoprostol 600mcg/pv > 96 hours
Outcomes	complete, incomplete abortion, side effects
Notes	only data from phase 1 are included, phase 2 was non-random no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Wiebe 2004

Methods	computer generated random list; sealed opaque envelopes
Participants	309 women at </=7 weeks of gestation confirmed by ultrasound; average age 27 years; average gestational age 42 days. Exclusion criteria: haemoglobin<9.5 g/L, seizure disease ,active liver disease, renal insufficiency, allergy/ intolerance to study medication. Study conducted at University of British Colombia, Canada
Interventions	methotrexate 50 mg/m2 followed 72- 144 hours later by: group 1: misoprostol 600mcg buccal (insert between their cheeks and leave for 1 h) group2: misoprostol 600mcg vaginal both groups instructed to repeat the dose 24 hours later if no heavy bleeding had occurred
Outcomes	successful abortion; side-effects; acceptability
Notes	women with ongoing pregnancy at day 8 follow-up received 1-2 more doses of misoprostol

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - adequate

Wiebe 2006

Methods	'randomised'
Participants	300 women with</= 7 weeks gestation confirmed by ultrasound. Patient characteristics not reported ('similar between groups')
Interventions	group 1: methotrexate 50mg/ m2 followed >/ 72 hours by misoprostol 400mcg vaginally

Wiebe 2006 *(Continued)*

	group 2: misoprostol 400mcg sublingual AND 400 mcg vaginal
Outcomes	complete abortion, side effects, acceptability
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Winikoff 2008

Methods	computer generated random assignment; random blocs of eight
Participants	966 women > 18 years old were enrolled. no contraindication to study medication, ≤ 63 days since LMP, access to telephone and emergency transportation. Geatational age confirmed by ultrasound if needed. Between September 2006 - May 2007. Study conducted at seven family planning centres: New York, Chicago, Pittsburgh, Waco, Austin, Boston; USA.
Interventions	mifepristone 200mcg followed 24-26 hours later at home by: 1) misoprostol 800mg orally, 2) 800mg misoprostol buccal (2X200mg in each cheek to keep for 30 minutes and swallow the remnants)
Outcomes	
Notes	results presented as per protocol analysis; successful abortion was defined as: without need for surgical intervention, regardless of how many doses of misoprostol needed. 14 women in the bucacal group and 13 in the oral group received a second dose of misoprostol.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - sealed opaque envelopes

Wu 1993

Methods	randomisation sequence generated centrally
Participants	multicentre trial in 5 hospitals in Beijing, China 990 women ≤ 49 days of amenorrhoea, pregnancy confirmed by ultrasound, without medical disorders, contraindication for the study medication and IUD in situ
Interventions	group 1: day 1: mifepristone 200mg and tamoxifen 40 mg/po day 2: tamoxifen 40mg/po day 3: PGF2alpha /pv group 2: day 1: mifepristone 200mg and placebo/po day 2: placebo /po

Wu 1993 *(Continued)*

	day 3: PGF2 alpha/vaginally
Outcomes	complete, incomplete abortion, duration of bleeding, resuming of menses, side effects
Notes	58/990 women were excluded post-randomisation due to protocol violation no major complications were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Zheng 1989 MI600PGF2pv

Methods	publication includes 4 studies, 1 of them is a randomised trial, randomisation procedure not stated.
Participants	192 women, ≤ 49 days of pregnancy seeking abortion in China inclusion/exclusion criteria not stated Follow-up on day 8 or day 14
Interventions	group 1: mifepristone 600mg group 2: mifepristone 600mg and prostaglandin F2alpha 1mg/pv
Outcomes	complete and incomplete abortion, ongoing pregnancy, time until passing of conceptus
Notes	only data from trial 4 are included no mentioning of major complications

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

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

Study	Reason for exclusion
Ashok 2002	single cohort, no comparison group
Aubeny 2000	randomisation by day of admission
Cheng 1999	women up to 16 weeks of gestation are included
Creinin 1996 A	single cohort, no comparison group
Davis 1999	Data for one group (Methotrexate) was reported for all (randomised and non-randomised) women together

Study	Reason for exclusion
De Nonno 2000	not RCT
ICMR 2000	allocation concealment and randomisation not stated
Jacobson 1990	This study was not designed to achieve abortion: only to test an existing regimen for treatment of ulcer and its effect on early pregnancy
Martin 1998	intervention not in the scope of the review (oral contraceptives or methotrexate to shorten the duration of bleeding)
Ngai 2000	intervention not in the scope of the review (water and misoprostol compared to misoprostol alone)
Norman 1992	non-randomised and randomised outcomes presented together
Swahn 1994	single cohort, no comparison group
Tang 1999	intervention not in the scope of the review (oral contraceptives vs palcebo for effectiveness, bleeding duration)
Wiebe 2001	review

DATA AND ANALYSES

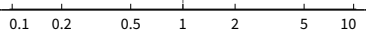
Comparison 1. combined regimen mifepristone/prostaglandin: dose of mifepristone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 all	6	6841	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.05]
1.2 600mg vs 200mg	4	3494	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.87, 1.32]
1.3 200mg vs 100 mg (>49 days)	1	1182	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.61, 1.29]
1.4 600mg vs 200mg with gemeprost 1mg/pv	2	1685	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.72, 1.45]
1.5 200mg vs 100 mg (</=49 days)	1	941	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.47, 1.33]
2 side effects	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 nausea	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

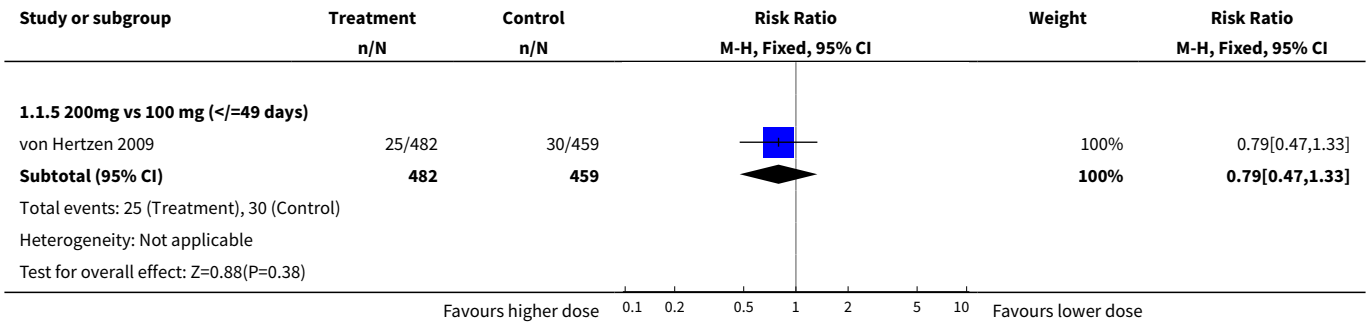
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 time until passing of conceptus > 3-6 hours	2	1116	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.74, 1.07]
4 ongoing pregnancy	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 surgical evacuation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 combined regimen mifepristone/prostaglandin: dose of mifepristone, Outcome 1 failure to achieve complete abortion.

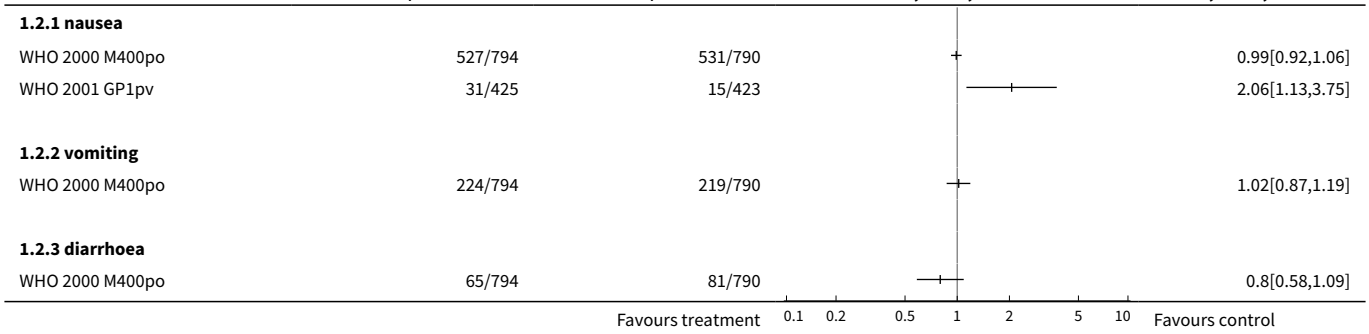
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 all					
McKinley 1993 M600po	7/110	7/110		2.25%	1[0.36,2.76]
von Hertzen 2009	72/1061	85/1062		27.27%	0.85[0.63,1.15]
WHO 2000 M400po	95/797	85/792		27.37%	1.11[0.84,1.46]
WHO 2001 GP1pv	37/447	34/449		10.89%	1.09[0.7,1.71]
WHO 1993 GP1pv	22/393	24/396		7.67%	0.92[0.53,1.62]
WHO 2001 MI200/50	51/650	72/574		24.55%	0.63[0.44,0.88]
Subtotal (95% CI)	**3458**	**3383**		**100%**	**0.9[0.77,1.05]**
Total events: 284 (Treatment), 307 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.54, df=5(P=0.18); I^2=33.71%					
Test for overall effect: Z=1.33(P=0.18)					
1.1.2 600mg vs 200mg					
McKinley 1993 M600po	7/110	7/110		4.66%	1[0.36,2.76]
WHO 2000 M400po	95/797	85/792		56.81%	1.11[0.84,1.46]
WHO 2001 GP1pv	37/447	34/449		22.6%	1.09[0.7,1.71]
WHO 1993 GP1pv	22/393	24/396		15.93%	0.92[0.53,1.62]
Subtotal (95% CI)	**1747**	**1747**		**100%**	**1.07[0.87,1.32]**
Total events: 161 (Treatment), 150 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.36, df=3(P=0.95); I^2=0%					
Test for overall effect: Z=0.64(P=0.52)					
1.1.3 200mg vs 100 mg (>49 days)					
von Hertzen 2009	47/579	55/603		100%	0.89[0.61,1.29]
Subtotal (95% CI)	**579**	**603**		**100%**	**0.89[0.61,1.29]**
Total events: 47 (Treatment), 55 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.61(P=0.54)					
1.1.4 600mg vs 200mg with gemeprost 1mg/pv					
WHO 2001 GP1pv	37/447	34/449		58.66%	1.09[0.7,1.71]
WHO 1993 GP1pv	22/393	24/396		41.34%	0.92[0.53,1.62]
Subtotal (95% CI)	**840**	**845**		**100%**	**1.02[0.72,1.45]**
Total events: 59 (Treatment), 58 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.65); I^2=0%					
Test for overall effect: Z=0.13(P=0.9)					



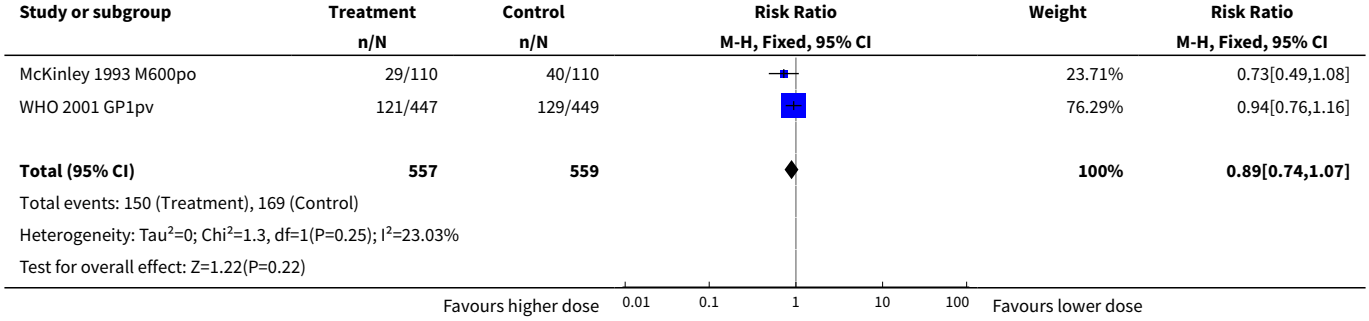
Favours higher dose — Favours lower dose



Analysis 1.2. Comparison 1 combined regimen mifepristone/ prostaglandin: dose of mifepristone, Outcome 2 side effects.



Analysis 1.3. Comparison 1 combined regimen mifepristone/prostaglandin: dose of mifepristone, Outcome 3 time until passing of conceptus > 3-6 hours.



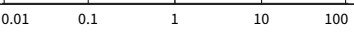
Analysis 1.4. Comparison 1 combined regimen mifepristone/ prostaglandin: dose of mifepristone, Outcome 4 ongoing pregnancy.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
McKinley 1993 M600po	0/110	1/110		0%	0.33[0.01,8.09]
von Hertzen 2009	8/1089	13/1092		0%	0.62[0.26,1.48]
WHO 2000 M400po	15/797	22/792		0%	0.68[0.35,1.3]
WHO 1993 GP1pv	1/393	2/396		0%	0.5[0.05,5.53]
WHO 2001 MI200/50	4/650	18/574		0%	0.2[0.07,0.58]

Favours higher dose — Favours lower dose

Analysis 1.5. Comparison 1 combined regimen mifepristone/ prostaglandin: dose of mifepristone, Outcome 5 surgical evacuation.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
von Hertzen 2009	19/1089	28/1092		0%	0.68[0.38,1.21]

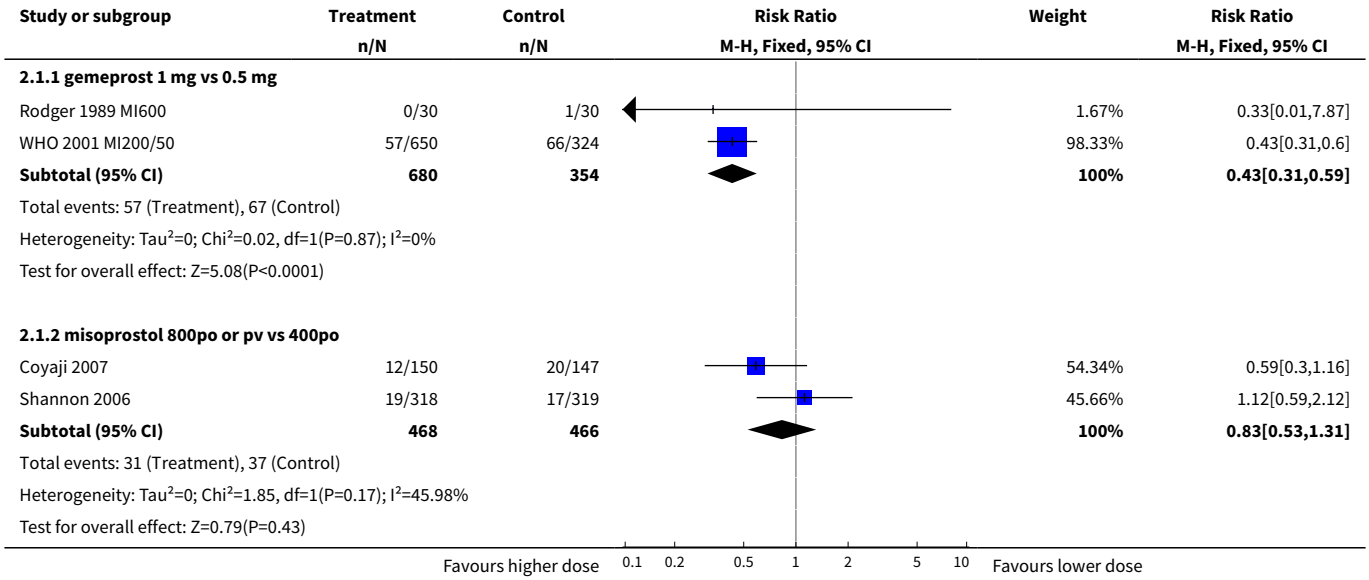


Favours higher dose — Favours lower dose

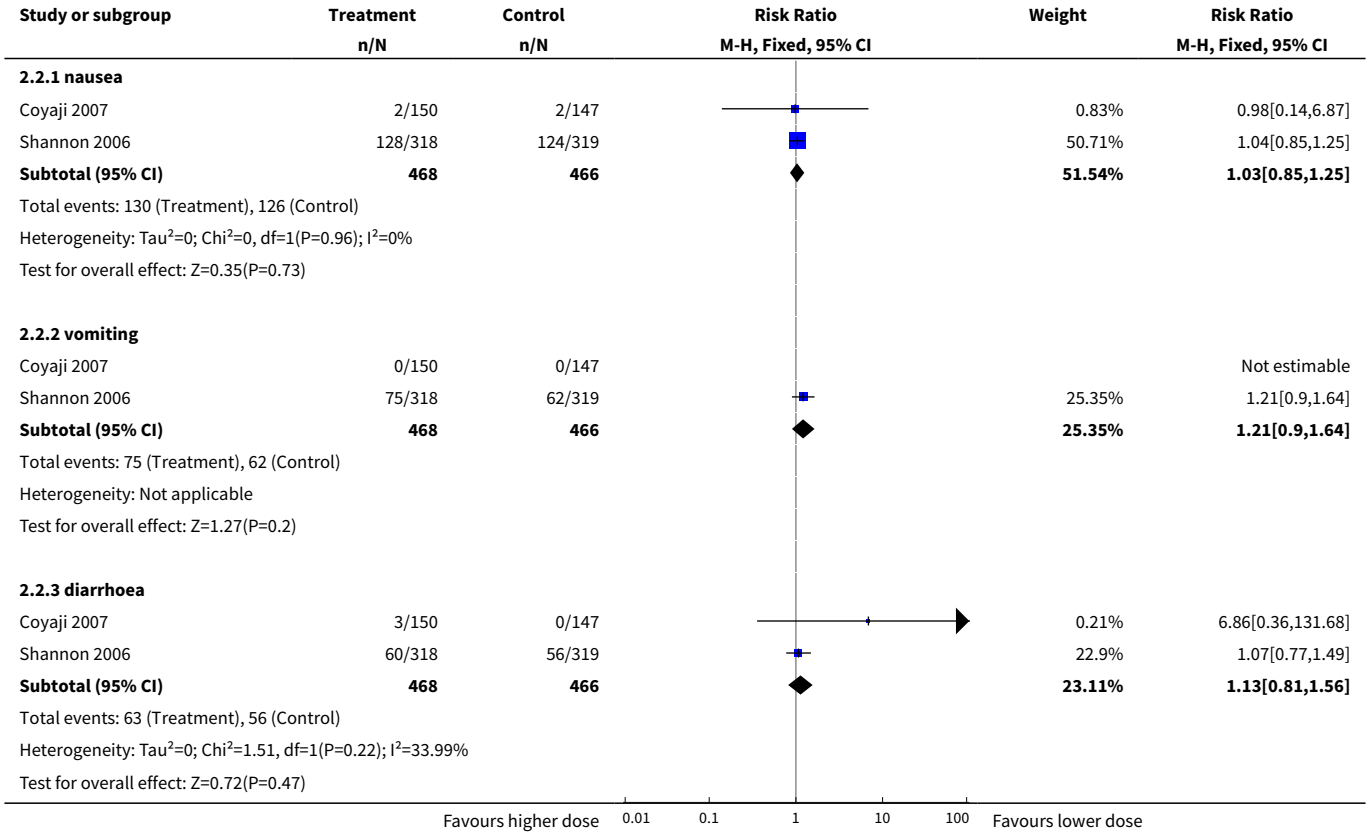
Comparison 2. combined regimen mifepristone/prostaglandin: dose of prostaglandin

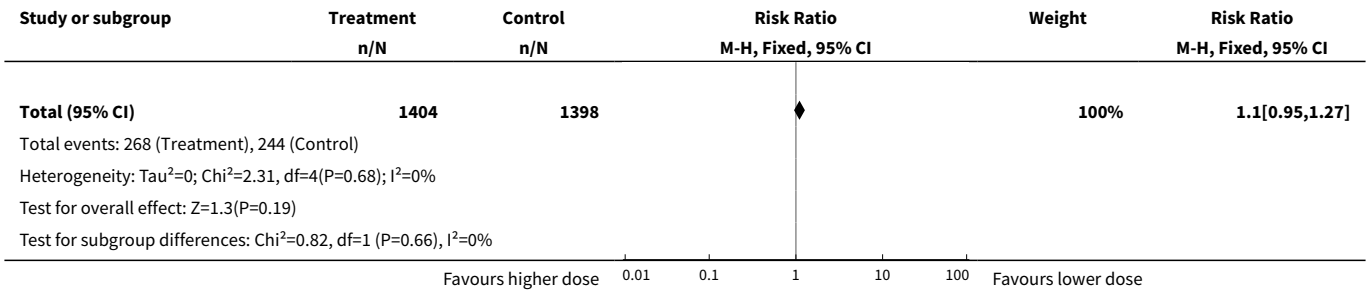
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 gemeprost 1 mg vs 0.5 mg	2	1034	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.31, 0.59]
1.2 misoprostol 800po or pv vs 400po	2	934	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.53, 1.31]
2 side effects	2	2802	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.95, 1.27]
2.1 nausea	2	934	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.85, 1.25]
2.2 vomiting	2	934	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.90, 1.64]
2.3 diarrhoea	2	934	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.81, 1.56]
3 women dissatisfied with the procedure	2	931	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.76, 1.50]
4 ongoing pregnancy	2	933	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 0.76]
4.1 misoprostol 800mcg vs 400 mcg	2	933	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 0.76]
5 surgical evacuation	2	934	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.53, 1.31]
5.1 misoprostol 800mcg vs 400mcg	2	934	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.53, 1.31]

Analysis 2.1. Comparison 2 combined regimen mifepristone/prostaglandin: dose of prostaglandin, Outcome 1 failure to achieve complete abortion.

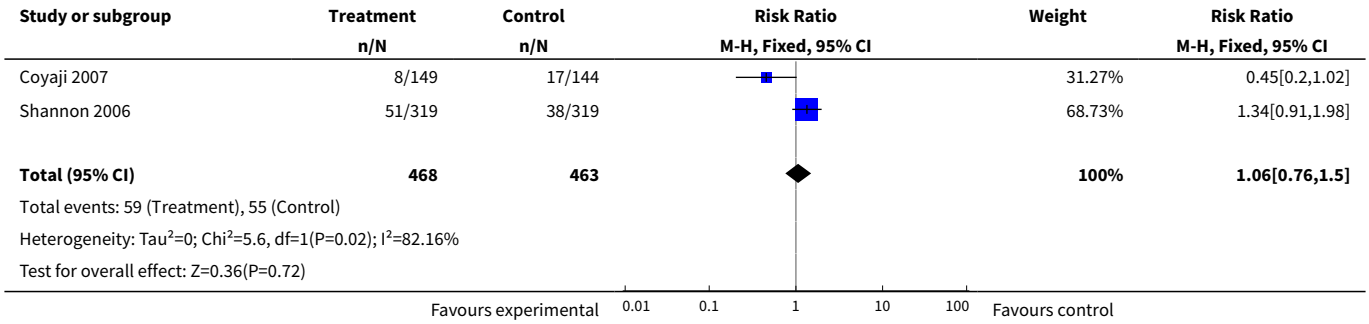


Analysis 2.2. Comparison 2 combined regimen mifepristone/ prostaglandin: dose of prostaglandin, Outcome 2 side effects.

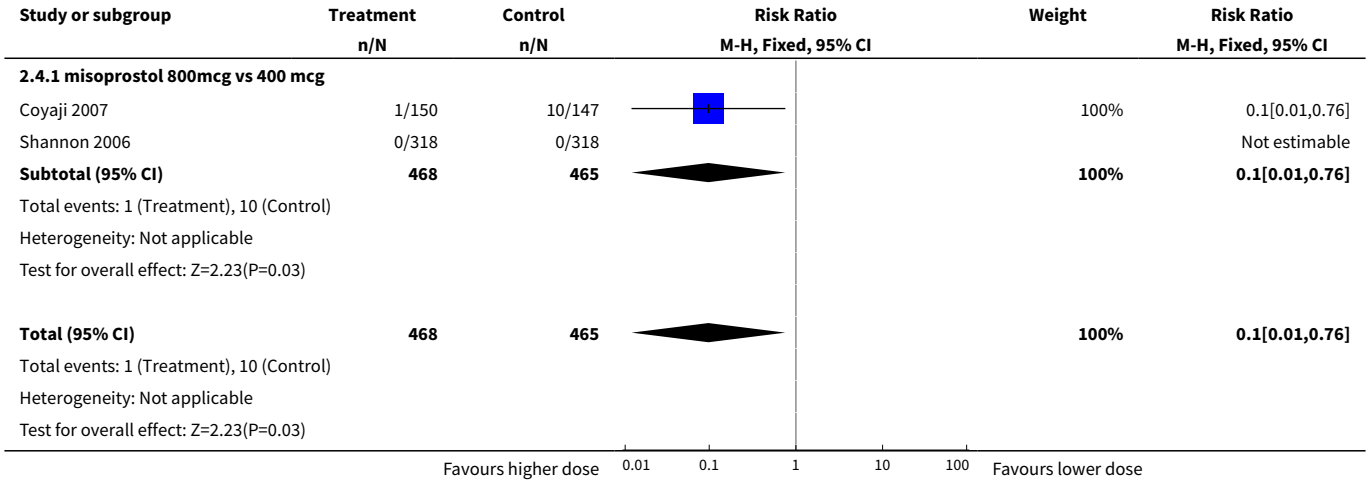




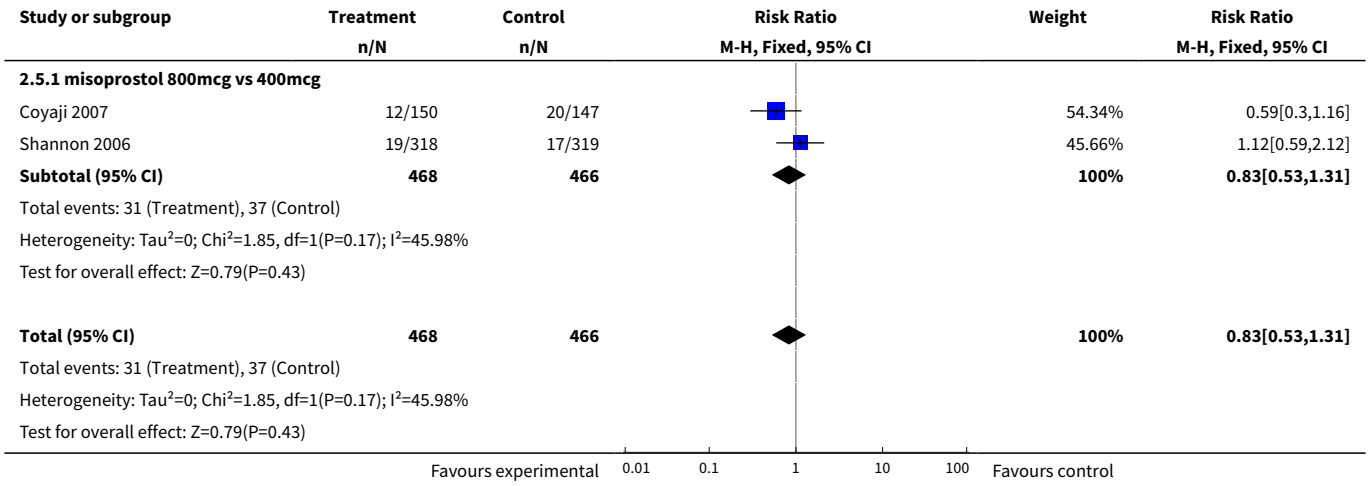
Analysis 2.3. Comparison 2 combined regimen mifepristone/prostaglandin: dose of prostaglandin, Outcome 3 women dissatisfied with the procedure.



Analysis 2.4. Comparison 2 combined regimen mifepristone/ prostaglandin: dose of prostaglandin, Outcome 4 ongoing pregnancy.



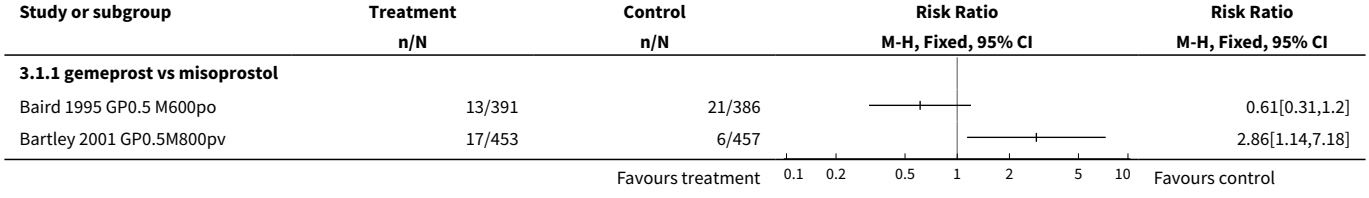
Analysis 2.5. Comparison 2 combined regimen mifepristone/prostaglandin: dose of prostaglandin, Outcome 5 surgical evacuation.

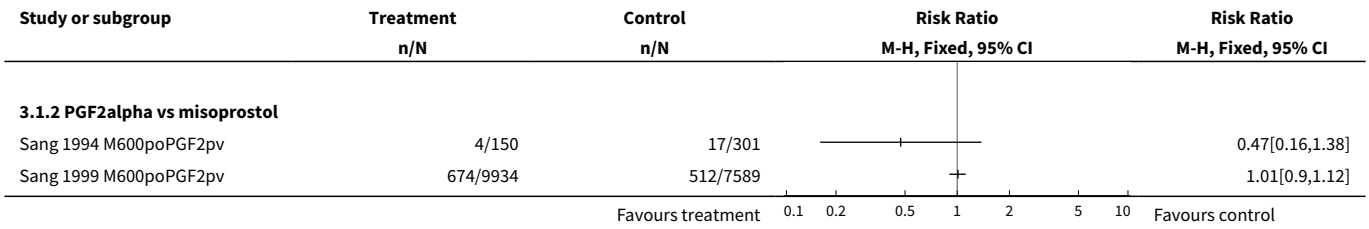


Comparison 3. combined regimen mifepristone/prostaglandin: type of prostaglandin

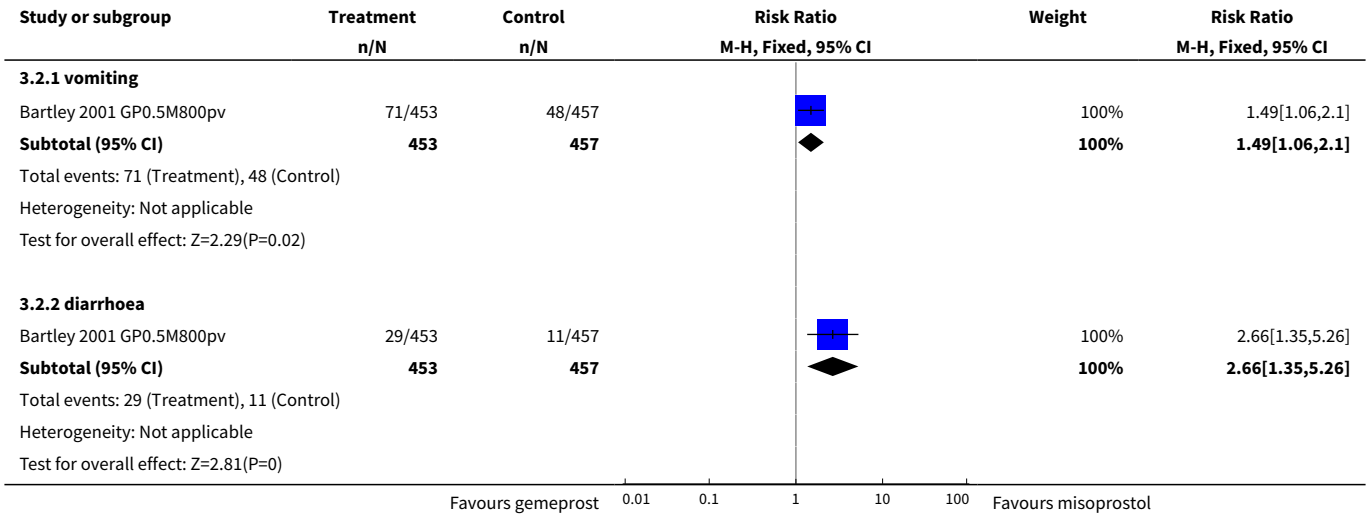
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 gemeprost vs misoprostol	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 PGF2alpha vs misoprostol	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 vomiting	1	910	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.06, 2.10]
2.2 diarrhoea	1	910	Risk Ratio (M-H, Fixed, 95% CI)	2.66 [1.35, 5.26]
3 ongoing pregnancy	2	1687	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.28, 1.48]
4 time until passing of conceptus > 3-6 hours	1	910	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.23]

Analysis 3.1. Comparison 3 combined regimen mifepristone/prostaglandin: type of prostaglandin, Outcome 1 failure to achieve complete abortion.

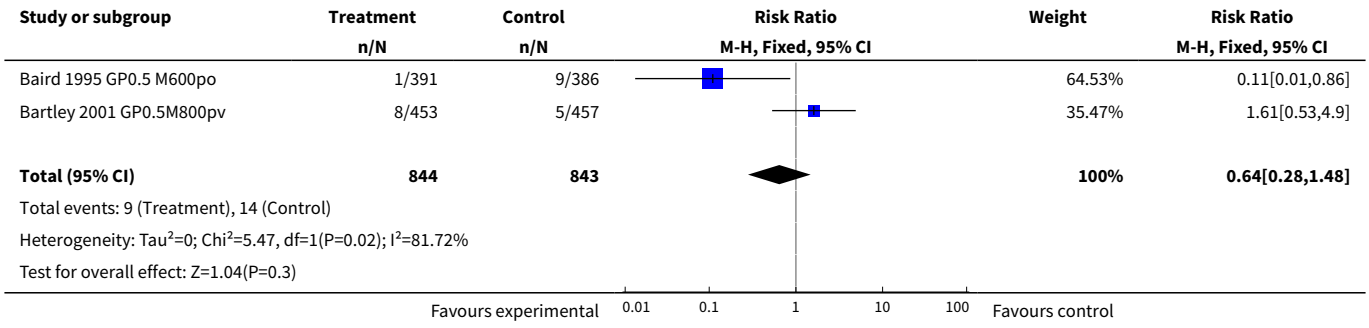




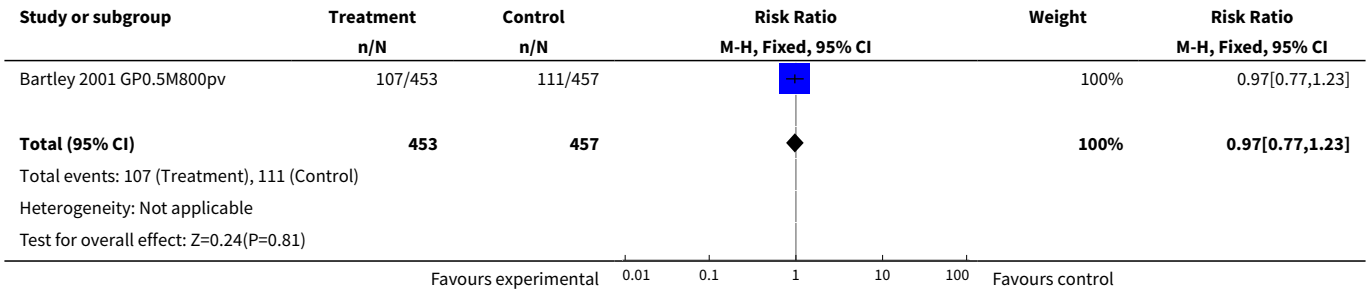
Analysis 3.2. Comparison 3 combined regimen mifepristone/ prostaglandin: type of prostaglandin, Outcome 2 side effects.



Analysis 3.3. Comparison 3 combined regimen mifepristone/ prostaglandin: type of prostaglandin, Outcome 3 ongoing pregnancy.



Analysis 3.4. Comparison 3 combined regimen mifepristone/prostaglandin: type of prostaglandin, Outcome 4 time until passing of conceptus > 3-6 hours.



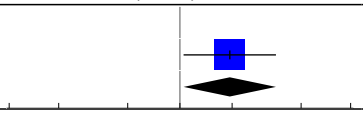
Comparison 4. combined regimen mifepristone/prostaglandin: time of prostaglandin

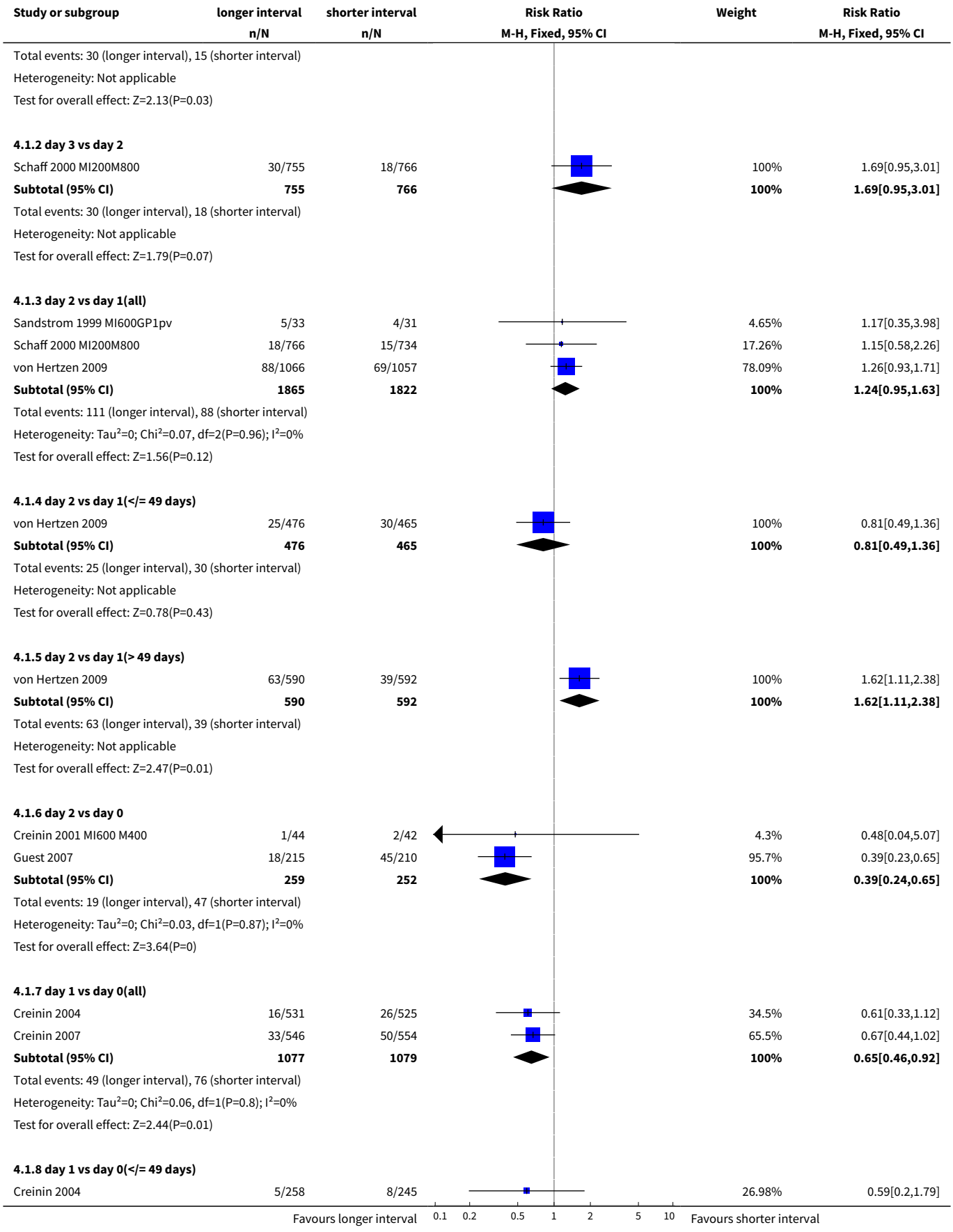
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 day 3 vs day 1	1	1489	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.05, 3.58]
1.2 day 3 vs day 2	1	1521	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.95, 3.01]
1.3 day 2 vs day 1(all)	3	3687	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.95, 1.63]
1.4 day 2 vs day 1(</= 49 days)	1	941	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.49, 1.36]
1.5 day 2 vs day 1(> 49 days)	1	1182	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.11, 2.38]
1.6 day 2 vs day 0	2	511	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.24, 0.65]
1.7 day 1 vs day 0(all)	2	2156	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.46, 0.92]
1.8 day 1 vs day 0(</= 49 days)	2	998	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.38, 1.14]
1.9 day 1 vs day 0(> 49 days)	2	1158	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.41, 1.06]
2 side effects	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 nausea day 3 vs day 1	1	1358	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.96, 1.14]
2.2 nausea day 3 vs day 2	1	1384	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.06]
2.3 nausea day 2 vs day 1	1	1434	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.98, 1.16]
2.4 nausea day 2 vs day 0	2	444	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.58, 1.11]
2.5 vomiting day 3 vs day 1	1	1358	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.19]
2.6 vomiting day 3 vs day 2	1	1384	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.13]
2.7 vomiting day 2 vs day 1	1	1434	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.90, 1.22]

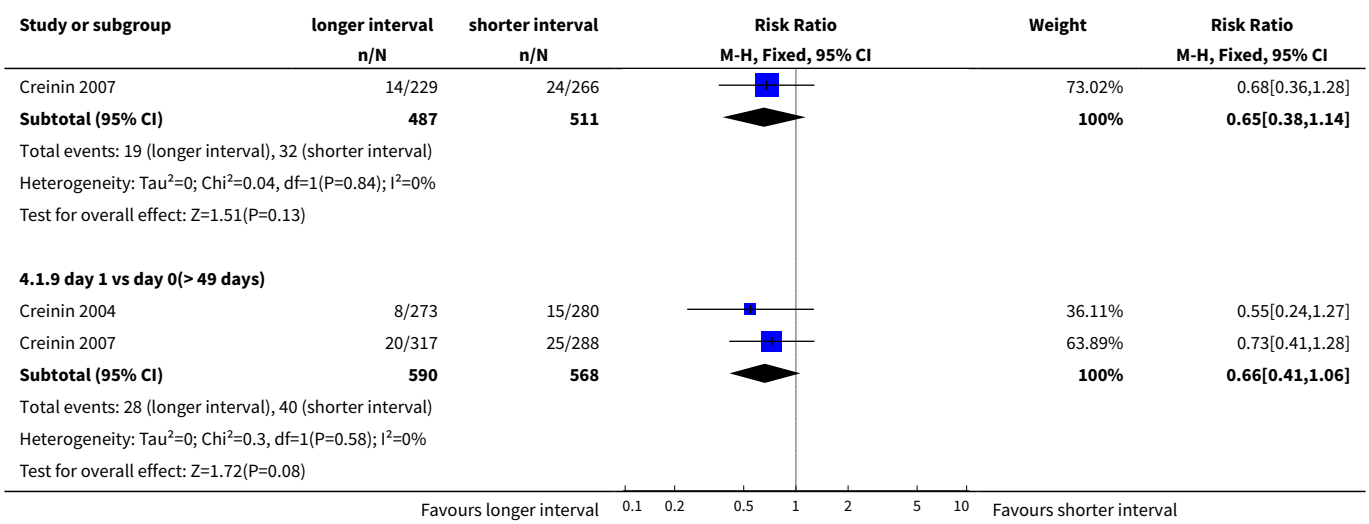
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8 vomiting day 2 vs day 0	2	444	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.59, 1.36]
2.9 diarrhoea day 3 vs day 1	1	1358	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.99, 1.48]
2.10 diarrhoea day 3 vs day 2	1	1384	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.95, 1.42]
2.11 diarrhoea day 2 vs day 1	1	1434	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.85, 1.28]
2.12 diarrhoea day 2 vs day 0	2	444	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.41, 1.03]
2.13 nausea day 1 vs day 0	2	2137	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.31]
2.14 vomiting day 1 vs day 0	2	2137	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.79, 1.62]
2.15 diarrhoea day 1 vs day 0	2	2137	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.58, 1.18]
3 surgical evacuation	5	8330	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.76, 1.27]
3.1 day 3 vs day 1	1	1489	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.78, 2.83]
3.2 day 3 vs day 2	1	1521	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.92, 3.52]
3.3 day 2 vs day 1	2	3681	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.68, 1.67]
3.4 day 2 vs day 0	2	511	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.19, 0.85]
3.5 day 1 vs day 0	1	1128	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.36, 1.20]
4 ongoing pregnancy	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 day 3 vs day 1	1	1489	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.51, 4.73]
4.2 day 3 vs day 2	1	1521	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [0.72, 10.16]
4.3 day 2 vs day 1 (all)	2	3681	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.45, 1.90]
4.4 day 1 vs day 0	2	2208	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.07, 1.66]
5 women dissatisfied with the procedure	1	1349	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.47]

Analysis 4.1. Comparison 4 combined regimen mifepristone/prostaglandin: time of prostaglandin, Outcome 1 failure to achieve complete abortion.

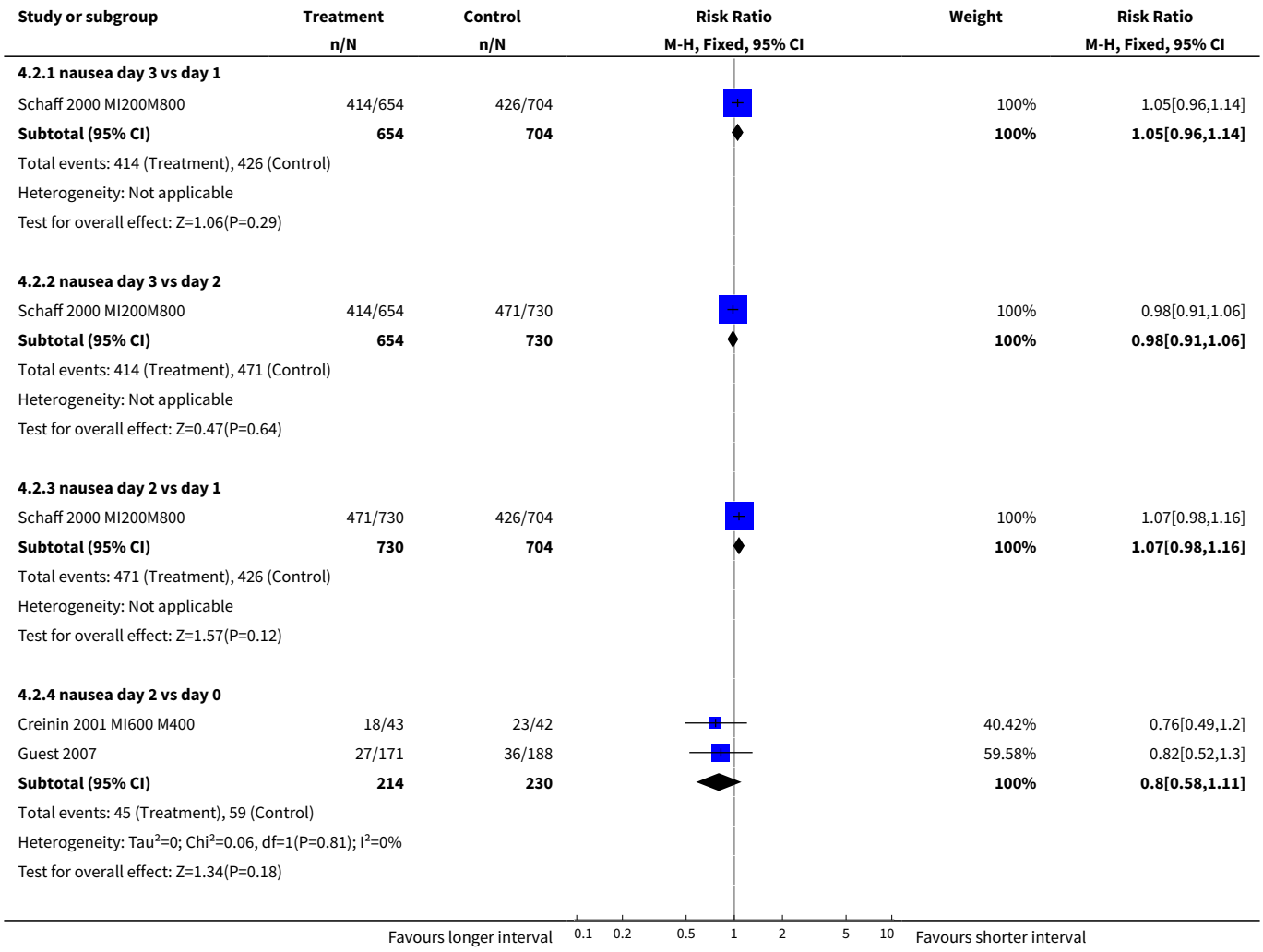
Study or subgroup	longer interval n/N	shorter interval n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 day 3 vs day 1					
Schaff 2000 MI200M800	30/755	15/734		100%	1.94[1.05,3.58]
Subtotal (95% CI)	**755**	**734**		**100%**	**1.94[1.05,3.58]**

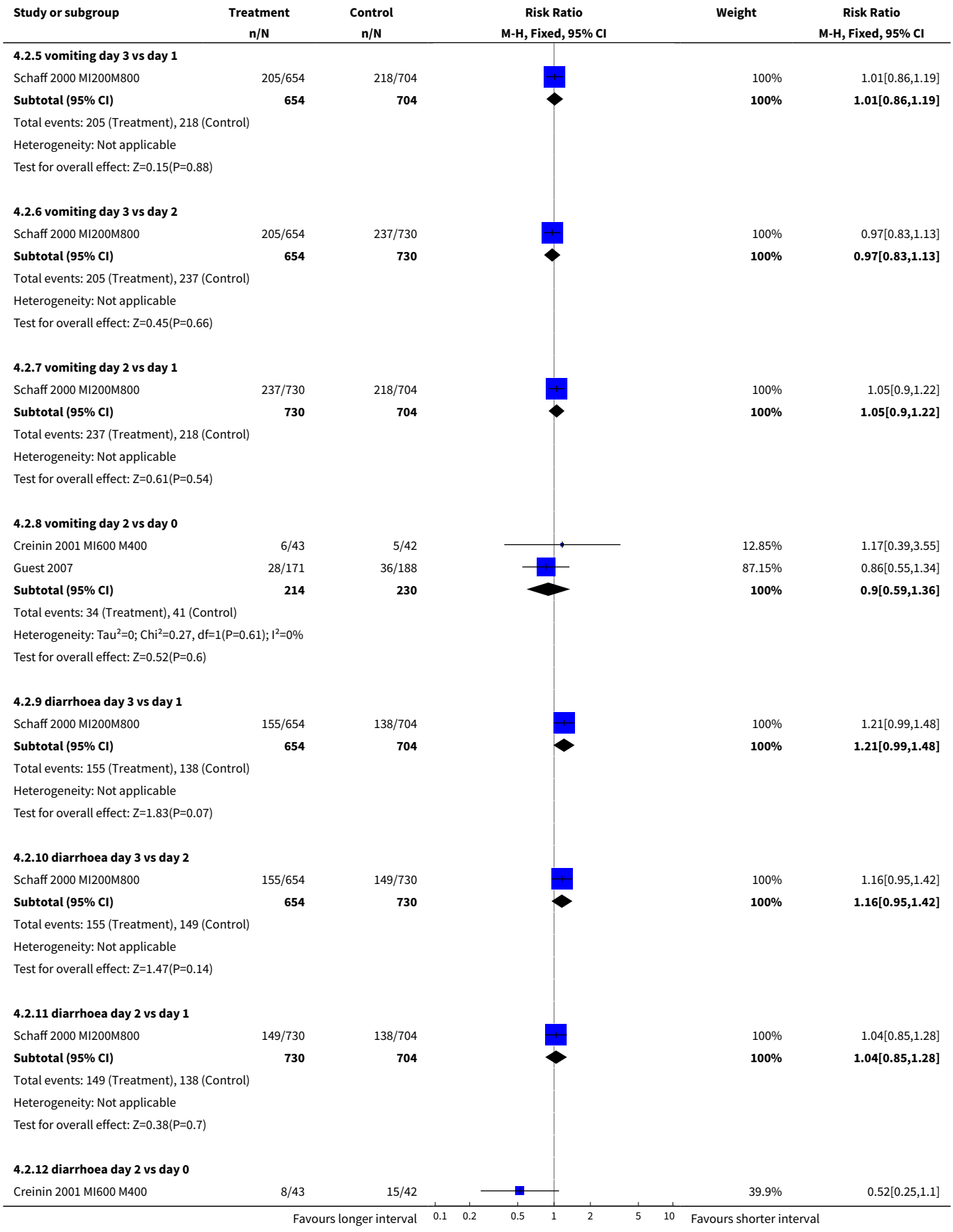


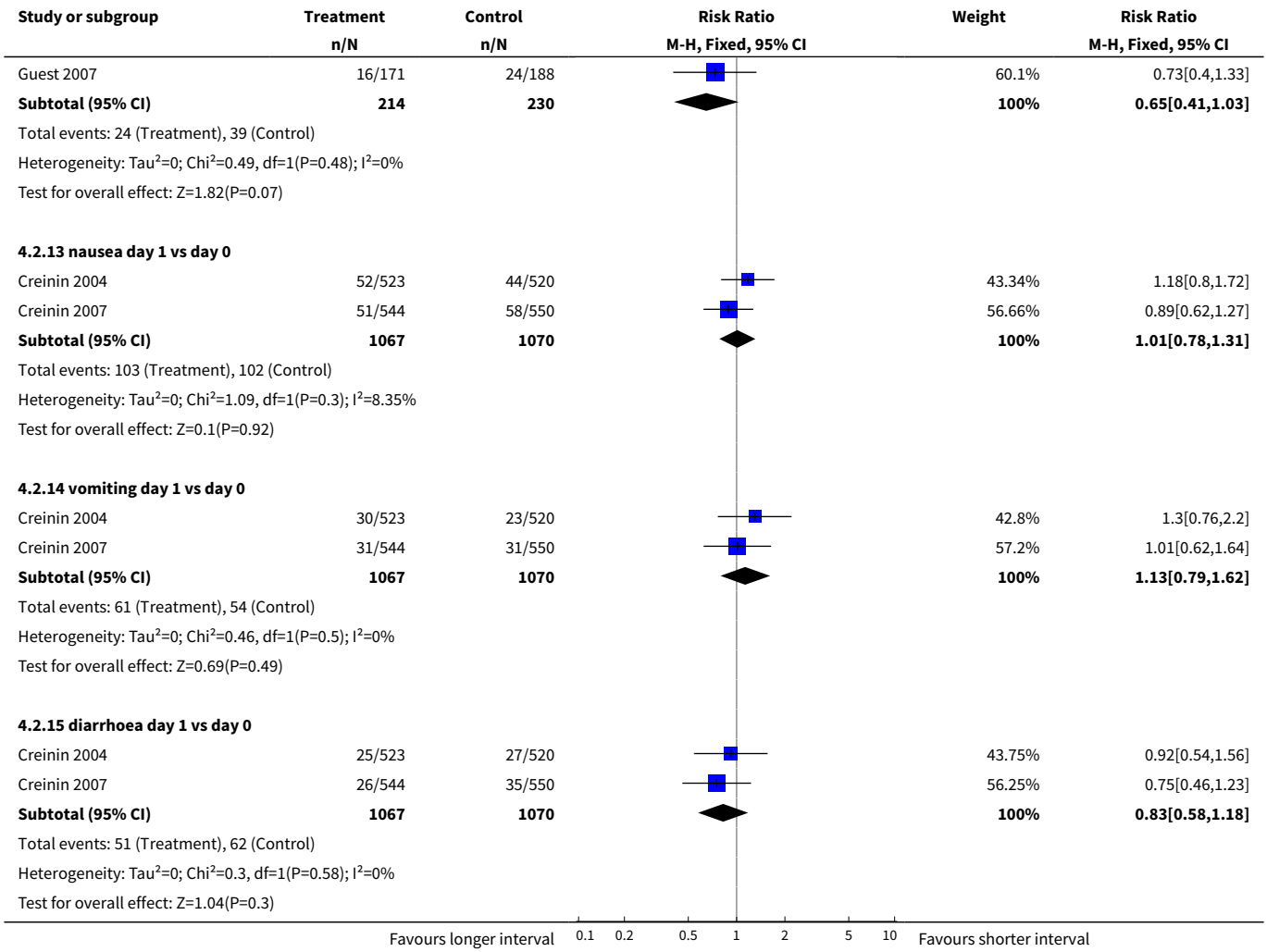




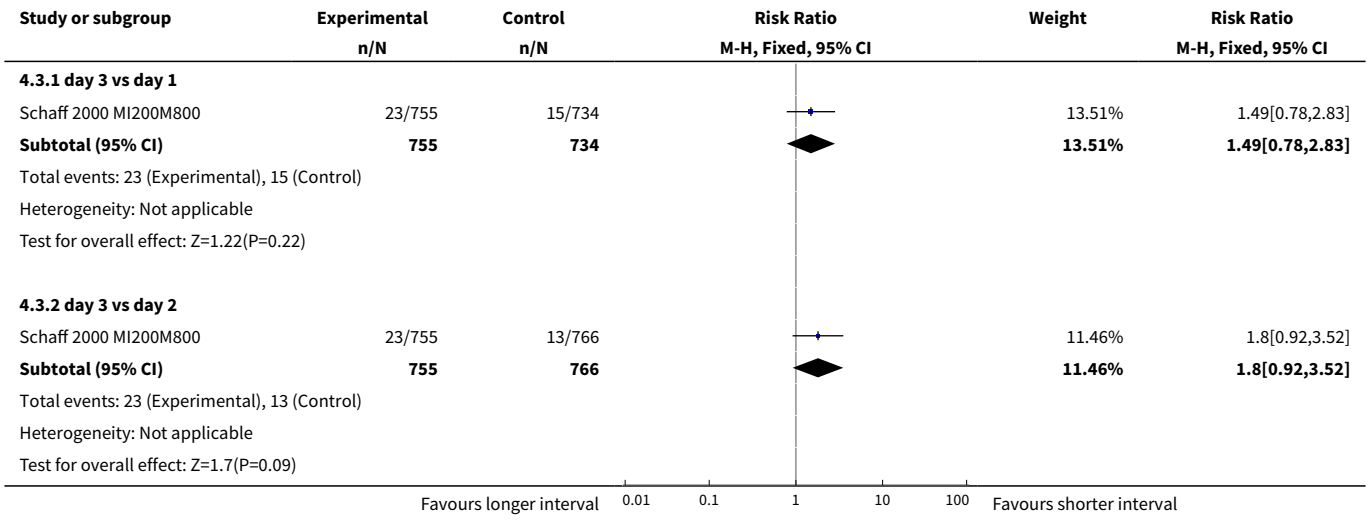
Analysis 4.2. Comparison 4 combined regimen mifepristone/ prostaglandin: time of prostaglandin, Outcome 2 side effects.

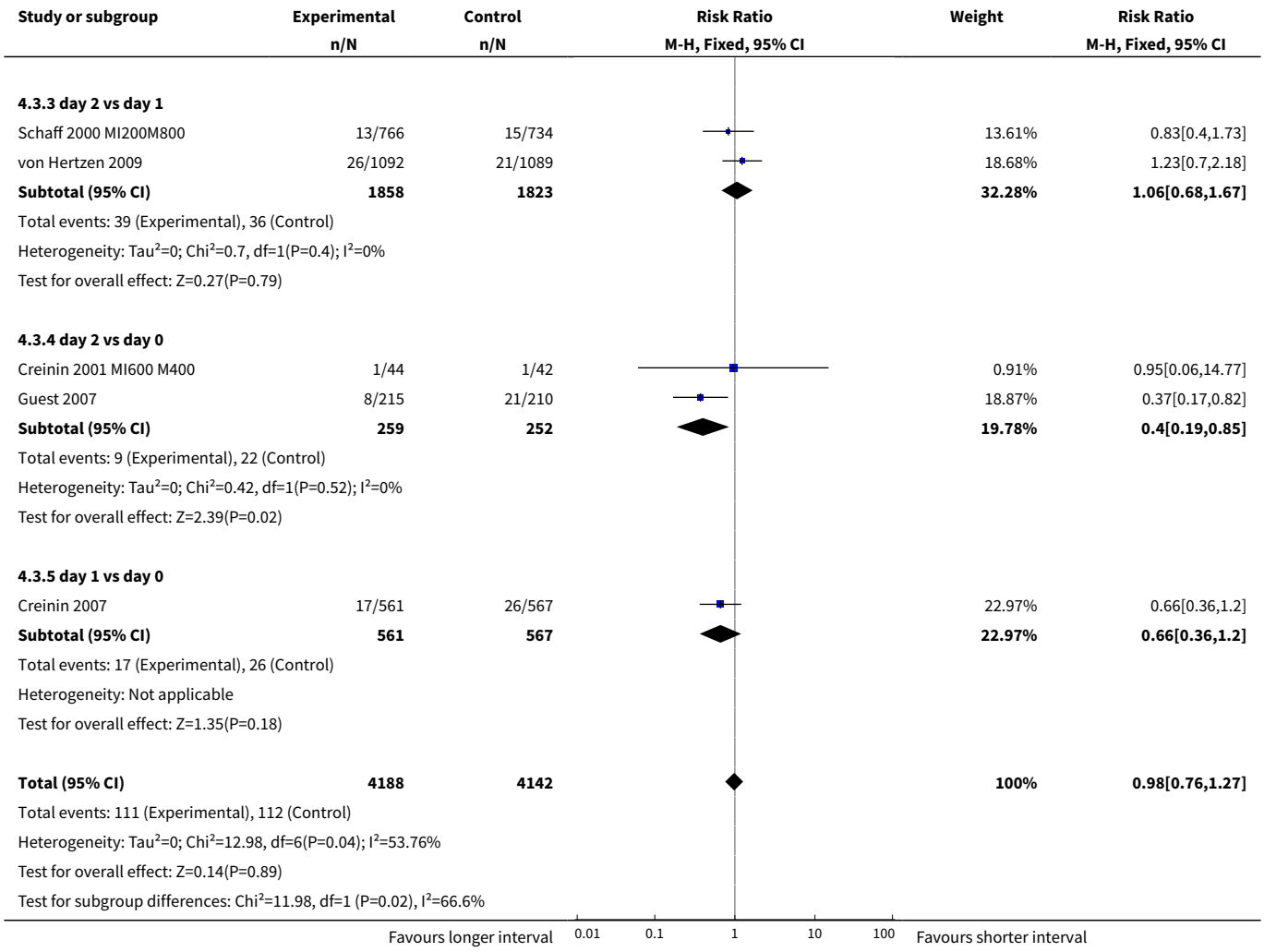




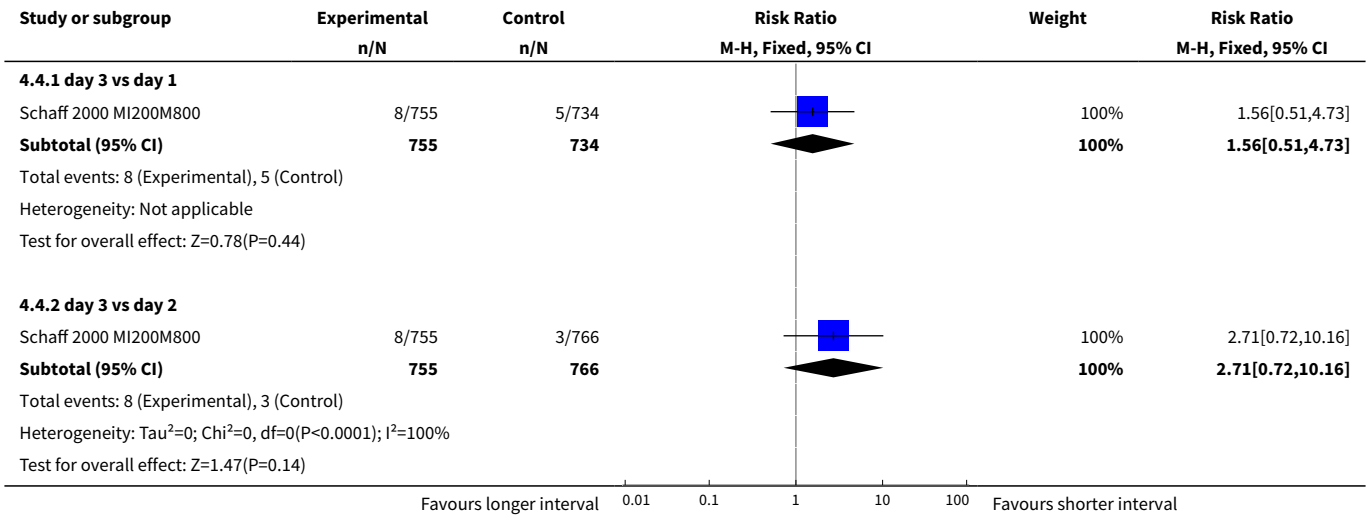


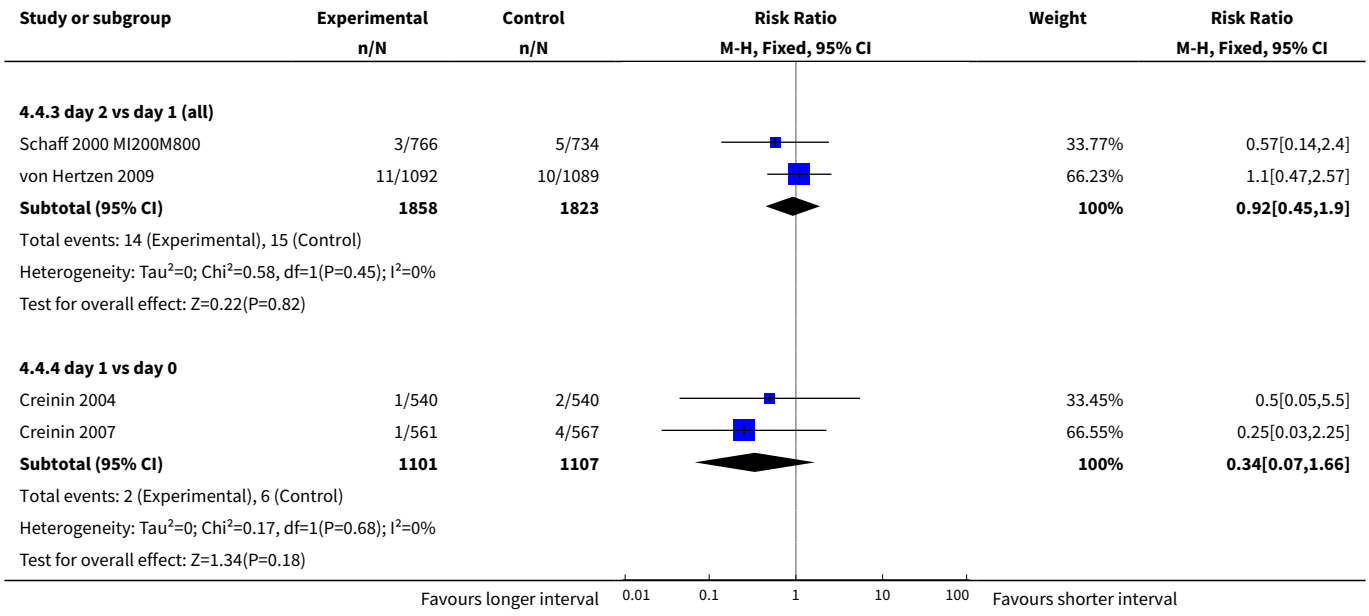
Analysis 4.3. Comparison 4 combined regimen mifepristone/ prostaglandin: time of prostaglandin, Outcome 3 surgical evacuation.



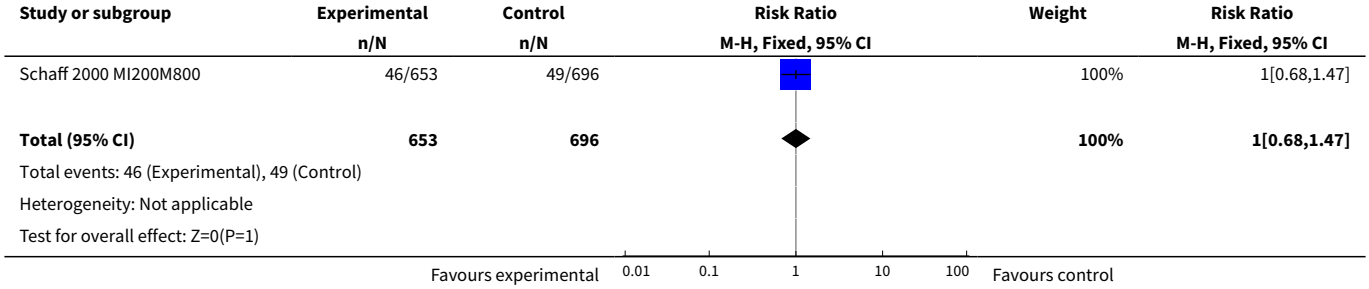


Analysis 4.4. Comparison 4 combined regimen mifepristone/ prostaglandin: time of prostaglandin, Outcome 4 ongoing pregnancy.





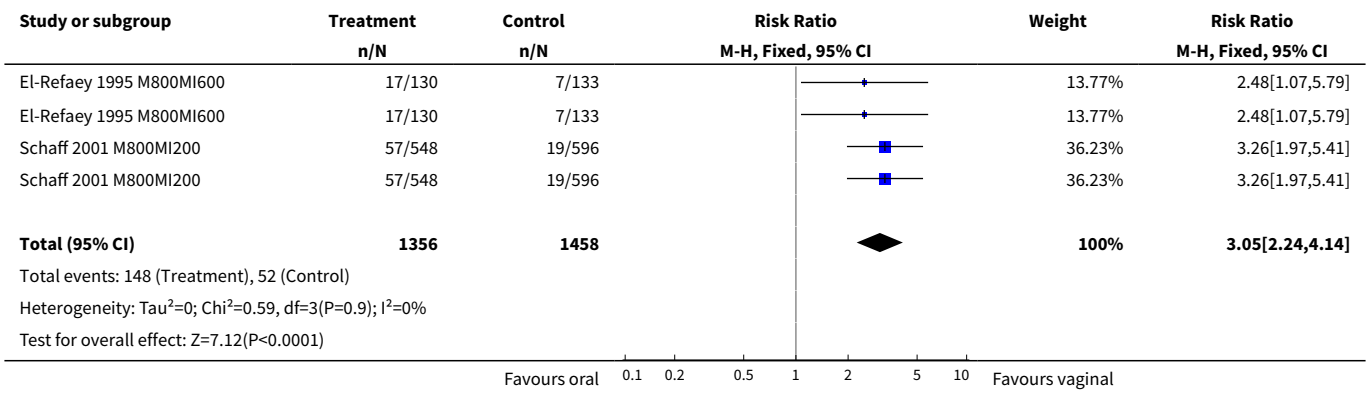
Analysis 4.5. Comparison 4 combined regimen mifepristone/prostaglandin: time of prostaglandin, Outcome 5 women dissatisfied with the procedure.



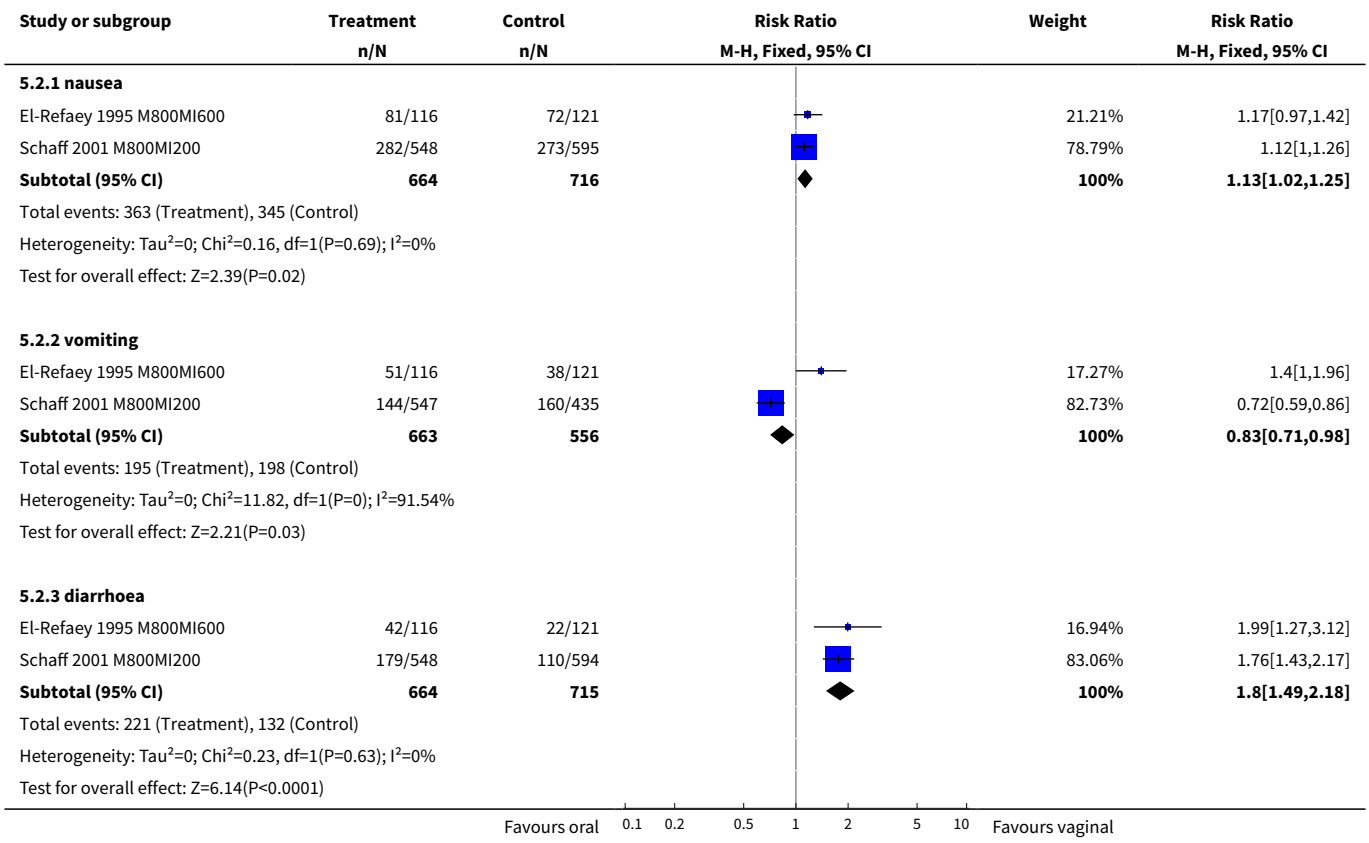
Comparison 5. combined regimen mifepristone/prostaglandin: misoprostol po vs pv

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	2	2814	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [2.24, 4.14]
2 side effects	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 nausea	2	1380	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.02, 1.25]
2.2 vomiting	2	1219	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.71, 0.98]
2.3 diarrhoea	2	1379	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.49, 2.18]

Analysis 5.1. Comparison 5 combined regimen mifepristone/prostaglandin: misoprostol po vs pv, Outcome 1 failure to achieve complete abortion.



Analysis 5.2. Comparison 5 combined regimen mifepristone/prostaglandin: misoprostol po vs pv, Outcome 2 side effects.



Comparison 6. combined regimen mifepristone/prostaglandin: misoprostol buccal vs pv

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1	429	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.36, 1.67]
2 side effects	1	1287	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.07, 1.36]
2.1 nausea	1	429	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.98, 1.29]
2.2 vomiting	1	429	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.89, 1.51]
2.3 diarrhoea	1	429	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.12, 2.03]

Analysis 6.1. Comparison 6 combined regimen mifepristone/prostaglandin: misoprostol buccal vs pv, Outcome 1 failure to achieve complete abortion.

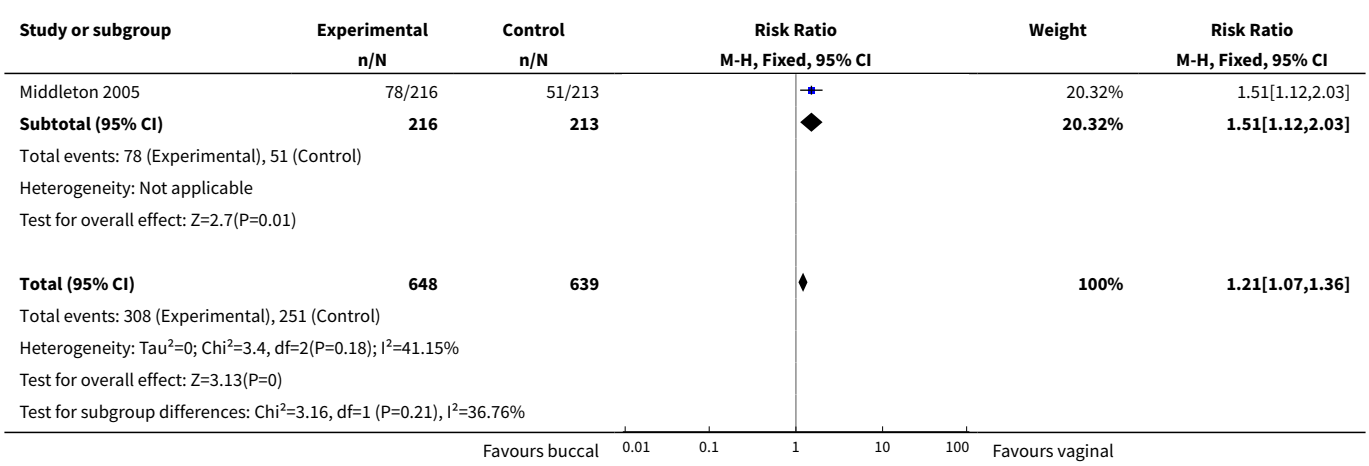
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Middleton 2005	11/216	14/213		100%	0.77[0.36,1.67]
Total (95% CI)	**216**	**213**		**100%**	**0.77[0.36,1.67]**
Total events: 11 (Experimental), 14 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.51)					

Favours buccal — Favours vaginal

Analysis 6.2. Comparison 6 combined regimen mifepristone/prostaglandin: misoprostol buccal vs pv, Outcome 2 side effects.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 nausea					
Middleton 2005	150/216	132/213		52.59%	1.12[0.98,1.29]
Subtotal (95% CI)	**216**	**213**		**52.59%**	**1.12[0.98,1.29]**
Total events: 150 (Experimental), 132 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.62(P=0.1)					
6.2.2 vomiting					
Middleton 2005	80/216	68/213		27.09%	1.16[0.89,1.51]
Subtotal (95% CI)	**216**	**213**		**27.09%**	**1.16[0.89,1.51]**
Total events: 80 (Experimental), 68 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.11(P=0.27)					
6.2.3 diarrhoea					

Favours buccal — Favours vaginal



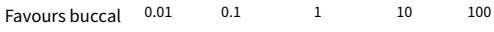
Comparison 7. combined regimen mifepristone/prostaglandin: misoprostol buccal vs oral

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 failure to achieve complete abortion (all)	1	847	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.40, 0.96]
1.2 failure to achieve complete abortion </= 49 days	1	418	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.25, 2.04]
1.3 failure to achieve complete abortion > 49 days	1	429	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.18, 0.73]
2 ongoing pregnancy	1	847	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.09, 0.82]
2.1 ongoing pregnancy </= 49 days	1	418	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.11, 3.80]
2.2 ongoing pregnancy >49 days	1	429	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.04, 0.78]
3 side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 nausea	1	830	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.01, 1.19]
3.2 vomiting	1	830	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.94, 1.27]
3.3 diarrhoea	1	830	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.94, 1.31]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4 women dissatisfied with the procedure	1	835	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.76, 1.91]

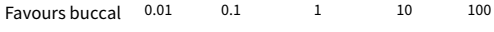
Analysis 7.1. Comparison 7 combined regimen mifepristone/prostaglandin: misoprostol buccal vs oral, Outcome 1 failure to achieve complete abortion.

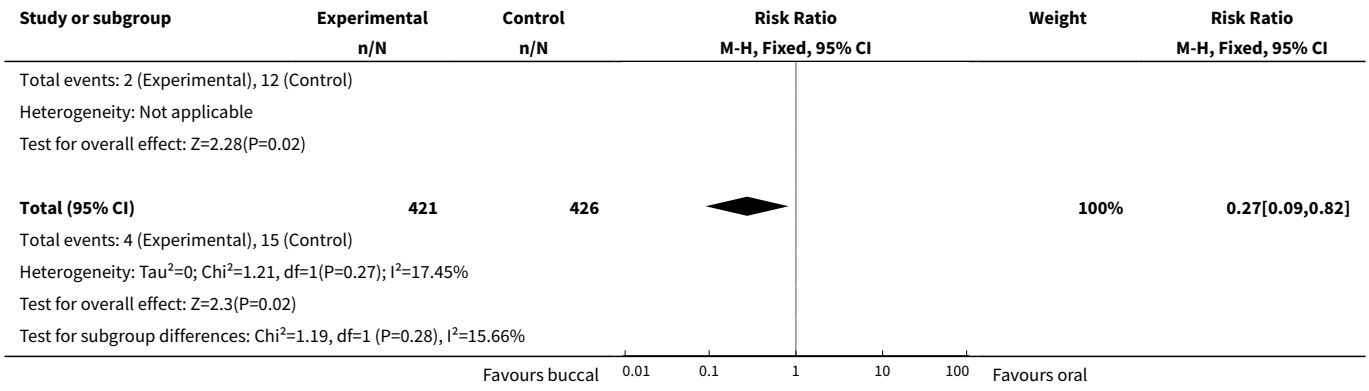
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 failure to achieve complete abortion (all)					
Winikoff 2008	30/421	49/426		100%	0.62[0.4,0.96]
Subtotal (95% CI)	**421**	**426**		**100%**	**0.62[0.4,0.96]**
Total events: 30 (Experimental), 49 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.16(P=0.03)					
7.1.2 failure to achieve complete abortion </= 49 days					
Winikoff 2008	6/213	8/205		100%	0.72[0.25,2.04]
Subtotal (95% CI)	**213**	**205**		**100%**	**0.72[0.25,2.04]**
Total events: 6 (Experimental), 8 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.61(P=0.54)					
7.1.3 failure to achieve complete abortion > 49 days					
Winikoff 2008	10/208	29/221		100%	0.37[0.18,0.73]
Subtotal (95% CI)	**208**	**221**		**100%**	**0.37[0.18,0.73]**
Total events: 10 (Experimental), 29 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.84(P=0)					



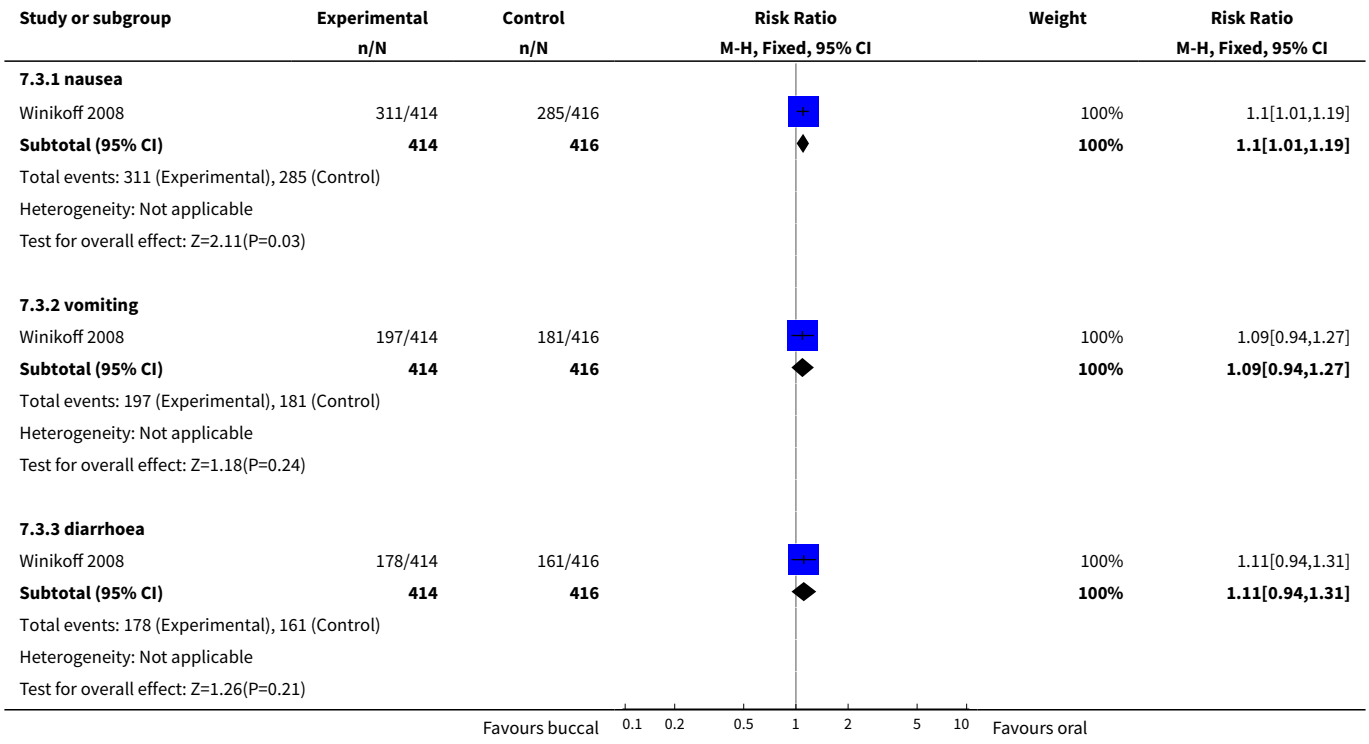
Analysis 7.2. Comparison 7 combined regimen mifepristone/ prostaglandin: misoprostol buccal vs oral, Outcome 2 ongoing pregnancy.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 ongoing pregnancy </= 49 days					
Winikoff 2008	2/213	3/205		20.81%	0.64[0.11,3.8]
Subtotal (95% CI)	**213**	**205**		**20.81%**	**0.64[0.11,3.8]**
Total events: 2 (Experimental), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.62)					
7.2.2 ongoing pregnancy >49 days					
Winikoff 2008	2/208	12/221		79.19%	0.18[0.04,0.78]
Subtotal (95% CI)	**208**	**221**		**79.19%**	**0.18[0.04,0.78]**

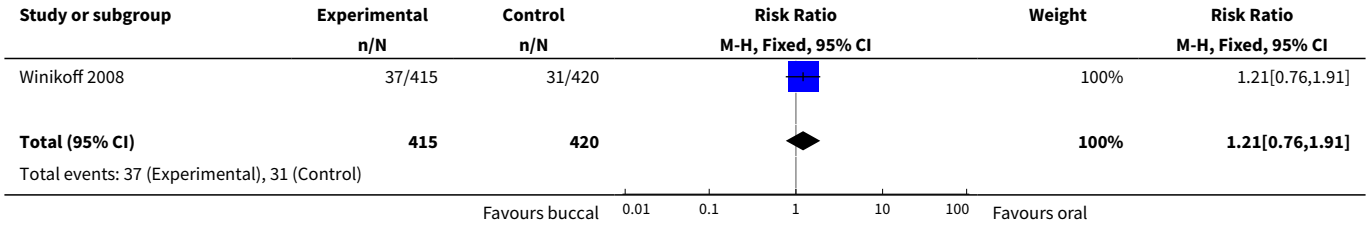


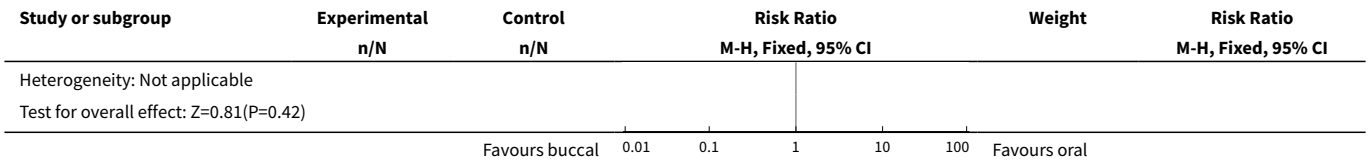


Analysis 7.3. Comparison 7 combined regimen mifepristone/ prostaglandin: misoprostol buccal vs oral, Outcome 3 side effects.



Analysis 7.4. Comparison 7 combined regimen mifepristone/prostaglandin: misoprostol buccal vs oral, Outcome 4 women dissatisfied with the procedure.

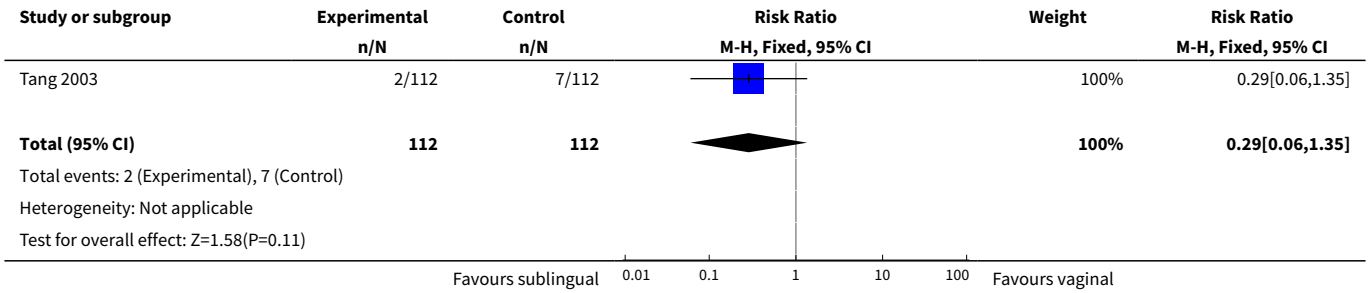




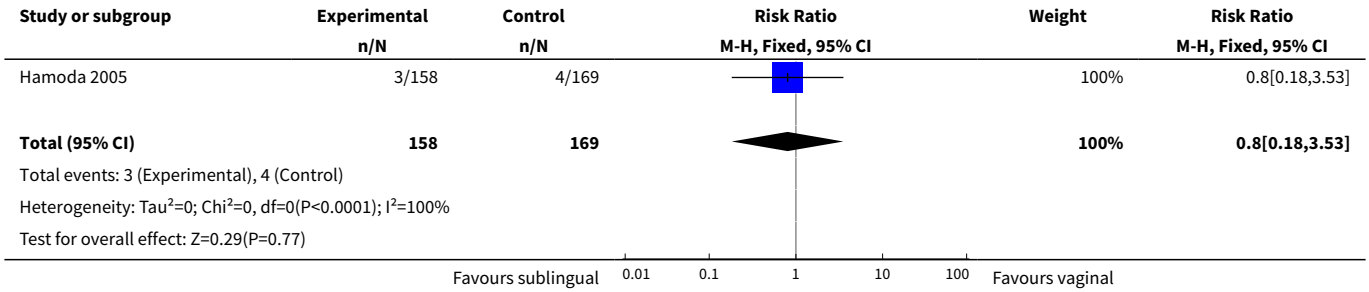
Comparison 8. combined regimen mifepristone/prostaglandin: misoprostol sublingual vs pv

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1	224	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.35]
2 surgical evacuation	1	327	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.18, 3.53]
3 ongoing pregnancy at follow-up	1	224	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.73]
4 side effects	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 nausea	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 vomiting	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 diarrhoea	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 women dissatisfied with the procedure	1	298	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [1.15, 6.87]
6 side effects	1	2490	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.02, 1.18]
6.1 nausea	1	830	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.01, 1.19]
6.2 vomiting	1	830	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.94, 1.27]
6.3 diarrhoea	1	830	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.94, 1.31]

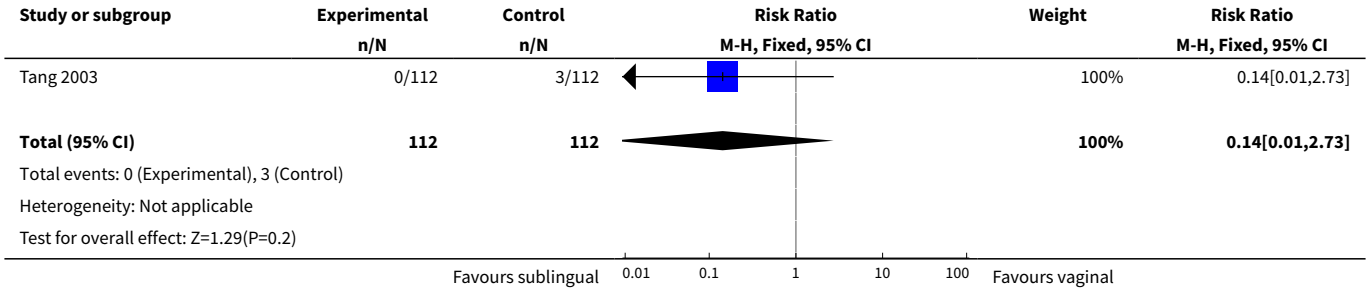
Analysis 8.1. Comparison 8 combined regimen mifepristone/prostaglandin: misoprostol sublingual vs pv, Outcome 1 failure to achieve complete abortion.



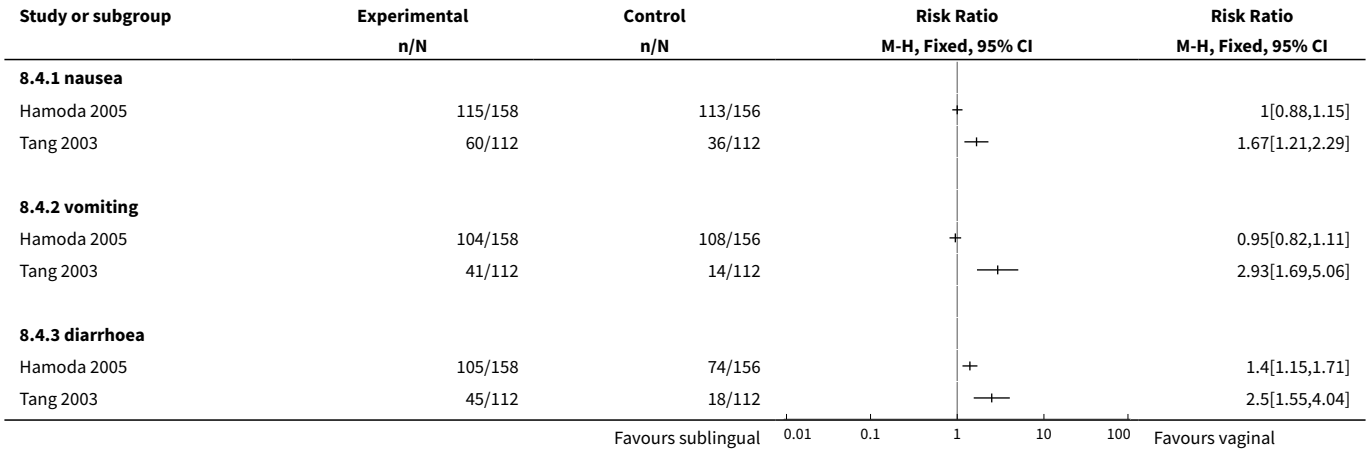
Analysis 8.2. Comparison 8 combined regimen mifepristone/prostaglandin: misoprostol sublingual vs pv, Outcome 2 surgical evacuation.



Analysis 8.3. Comparison 8 combined regimen mifepristone/prostaglandin: misoprostol sublingual vs pv, Outcome 3 ongoing pregnancy at follow-up.



Analysis 8.4. Comparison 8 combined regimen mifepristone/prostaglandin: misoprostol sublingual vs pv, Outcome 4 side effects.



Analysis 8.5. Comparison 8 combined regimen mifepristone/prostaglandin: misoprostol sublingual vs pv, Outcome 5 women dissatisfied with the procedure.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hamoda 2005	18/154	6/144		100%	2.81[1.15,6.87]
Total (95% CI)	**154**	**144**		**100%**	**2.81[1.15,6.87]**
Total events: 18 (Experimental), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.26(P=0.02)					

Analysis 8.6. Comparison 8 combined regimen mifepristone/prostaglandin: misoprostol sublingual vs pv, Outcome 6 side effects.

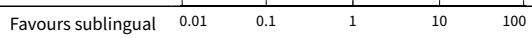
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.6.1 nausea					
Winikoff 2008	311/414	285/416		45.45%	1.1[1.01,1.19]
Subtotal (95% CI)	**414**	**416**		**45.45%**	**1.1[1.01,1.19]**
Total events: 311 (Experimental), 285 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.11(P=0.03)					
8.6.2 vomiting					
Winikoff 2008	197/414	181/416		28.87%	1.09[0.94,1.27]
Subtotal (95% CI)	**414**	**416**		**28.87%**	**1.09[0.94,1.27]**
Total events: 197 (Experimental), 181 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.18(P=0.24)					
8.6.3 diarrhoea					
Winikoff 2008	178/414	161/416		25.68%	1.11[0.94,1.31]
Subtotal (95% CI)	**414**	**416**		**25.68%**	**1.11[0.94,1.31]**
Total events: 178 (Experimental), 161 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.26(P=0.21)					
Total (95% CI)	**1242**	**1248**		**100%**	**1.1[1.02,1.18]**
Total events: 686 (Experimental), 627 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=2(P=0.99); I^2=0%					
Test for overall effect: Z=2.59(P=0.01)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.99), I^2=0%					

Comparison 9. combined regimen mifepristone/prostaglandin: misoprostol sublingual vs po

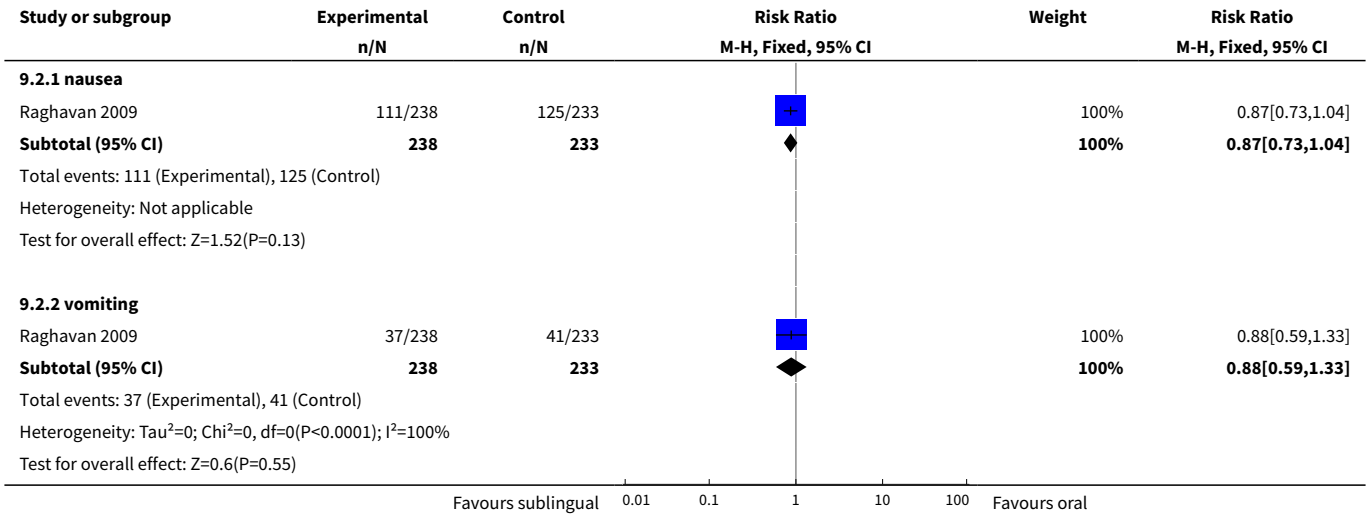
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 all	1	471	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.06, 0.72]
1.2 </= 49 days	1	422	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.08, 0.99]
1.3 > 49 days	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.60]
2 side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 nausea	1	471	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.73, 1.04]
2.2 vomiting	1	471	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.59, 1.33]
3 women dissatisfied with the procedure	1	471	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [0.94, 4.09]

Analysis 9.1. Comparison 9 combined regimen mifepristone/prostaglandin: misoprostol sublingual vs po, Outcome 1 failure to achieve complete abortion.

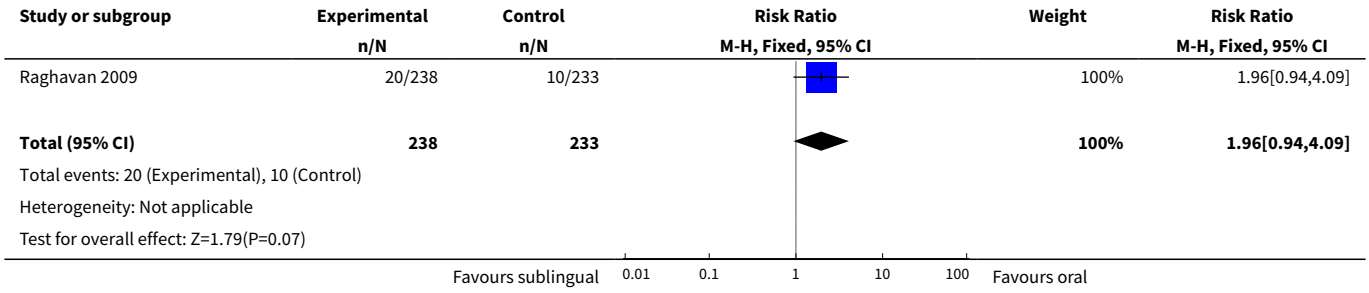
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.1 all					
Raghavan 2009	3/238	14/233		100%	0.21[0.06,0.72]
Subtotal (95% CI)	**238**	**233**		**100%**	**0.21[0.06,0.72]**
Total events: 3 (Experimental), 14 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.48(P=0.01)					
9.1.2 </= 49 days					
Raghavan 2009	3/208	11/214		100%	0.28[0.08,0.99]
Subtotal (95% CI)	**208**	**214**		**100%**	**0.28[0.08,0.99]**
Total events: 3 (Experimental), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.97(P=0.05)					
9.1.3 > 49 days					
Raghavan 2009	0/30	3/18		100%	0.09[0,1.6]
Subtotal (95% CI)	**30**	**18**		**100%**	**0.09[0,1.6]**
Total events: 0 (Experimental), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.64(P=0.1)					



Analysis 9.2. Comparison 9 combined regimen mifepristone/ prostaglandin: misoprostol sublingual vs po, Outcome 2 side effects.



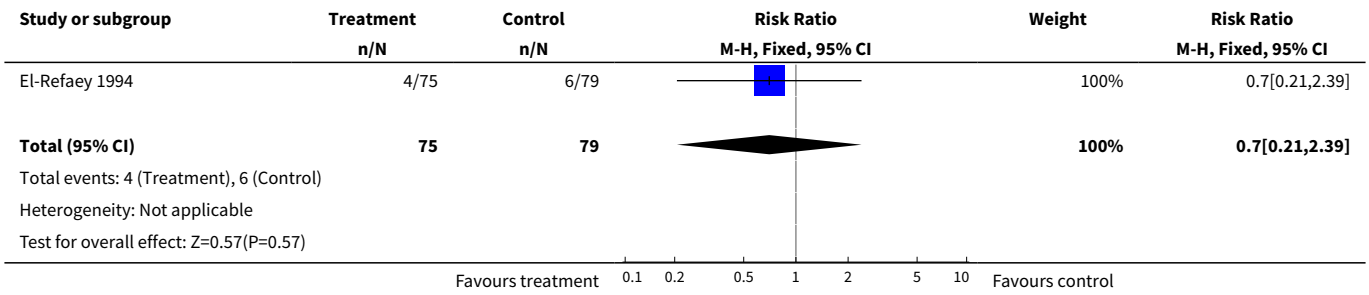
Analysis 9.3. Comparison 9 combined regimen mifepristone/prostaglandin: misoprostol sublingual vs po, Outcome 3 women dissatisfied with the procedure.



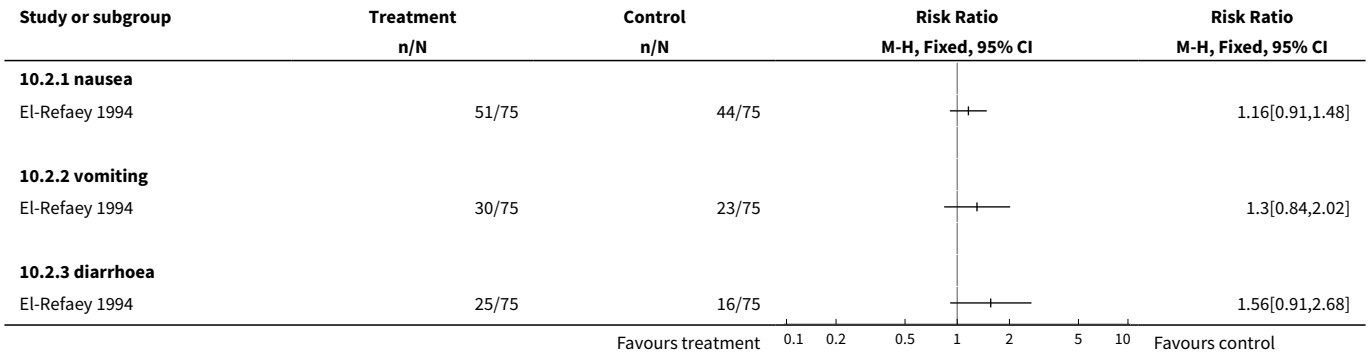
Comparison 10. combined regimen mifepristone/prostaglandin: single vs split dose prostaglandin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.21, 2.39]
2 side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 10.1. Comparison 10 combined regimen mifepristone/prostaglandin: single vs split dose prostaglandin, Outcome 1 failure to achieve complete abortion.



Analysis 10.2. Comparison 10 combined regimen mifepristone/ prostaglandin: single vs split dose prostaglandin, Outcome 2 side effects.



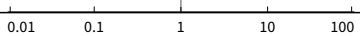
Comparison 11. combined regimen mifepristone/prostaglandin:single vs continuous prostaglandin

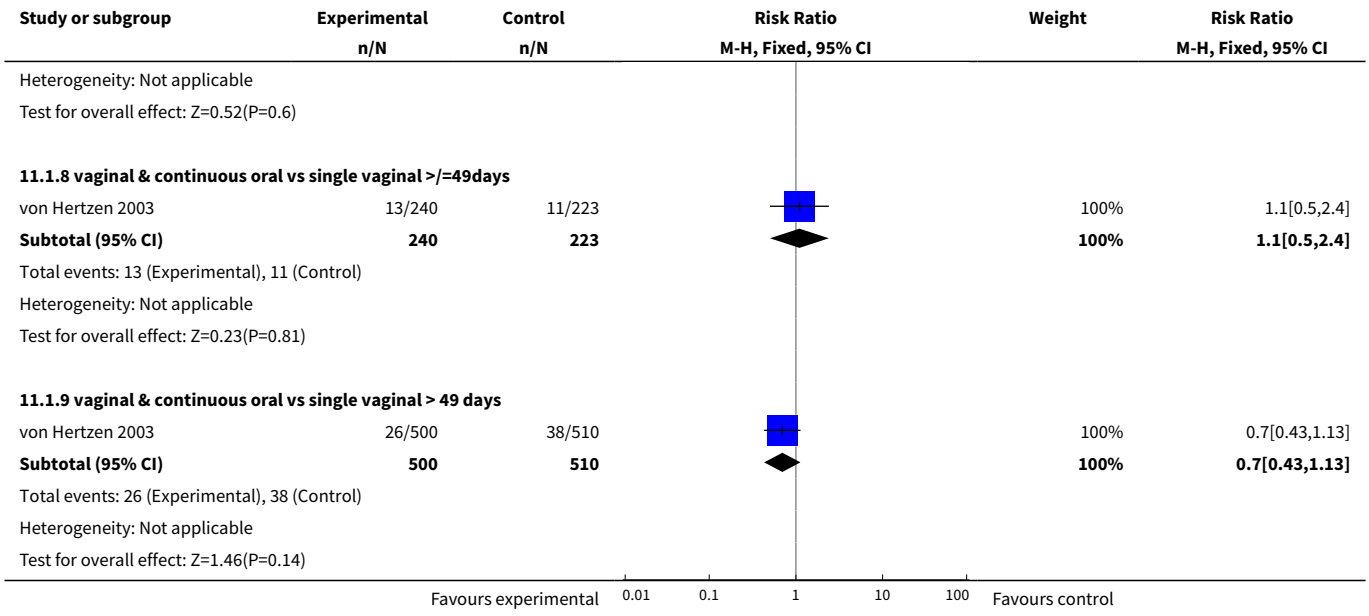
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 all oral vs vaginal & continuous oral	2	1581	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.01, 2.16]
1.2 all oral vs single vaginal	2	1578	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.83, 1.70]
1.3 vaginal & continuous oral vs single vaginal	2	1579	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.54, 1.19]
1.4 all oral vs vaginal & continuous oral </=49 days	1	476	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.57, 2.41]
1.5 all oral vs vaginal & continuous oral > 49 days	1	1004	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.00, 2.57]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.6 all oral vs single vaginal >/=49 days	1	459	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.60, 2.74]
1.7 all oral vs single vaginal > 49 days	1	1014	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.70]
1.8 vaginal & continuous oral vs single vaginal >/=49days	1	463	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.50, 2.40]
1.9 vaginal & continuous oral vs single vaginal > 49 days	1	1010	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.43, 1.13]
2 ongoing pregnancy at follow-up	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 all oral vs vaginal & continuous oral	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 all oral vs single vaginal	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 vaginal & continuous oral vs single vaginal	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 nausea	1	4438	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.83, 1.12]
3.1 all oral vs vaginal & continuous oral	1	1481	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.65, 1.09]
3.2 all oral vs single vaginal	1	1478	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.72, 1.24]
3.3 vaginal & continuous oral vs single vaginal	1	1479	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.87, 1.45]
4 vomiting	1	4438	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.21]
4.1 all oral vs vaginal & continuous oral	1	1481	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.49, 1.30]
4.2 all oral vs single vaginal	1	1478	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.53, 1.43]
4.3 vaginal & continuous oral vs single vaginal	1	1479	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.68, 1.74]
5 diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 all oral vs vaginal & continuous oral	1	1481	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.11, 3.01]
5.2 all oral vs single vaginal	1	1478	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.24, 3.53]
5.3 vaginal & continuous oral vs single vaginal	1	1479	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.63, 2.07]

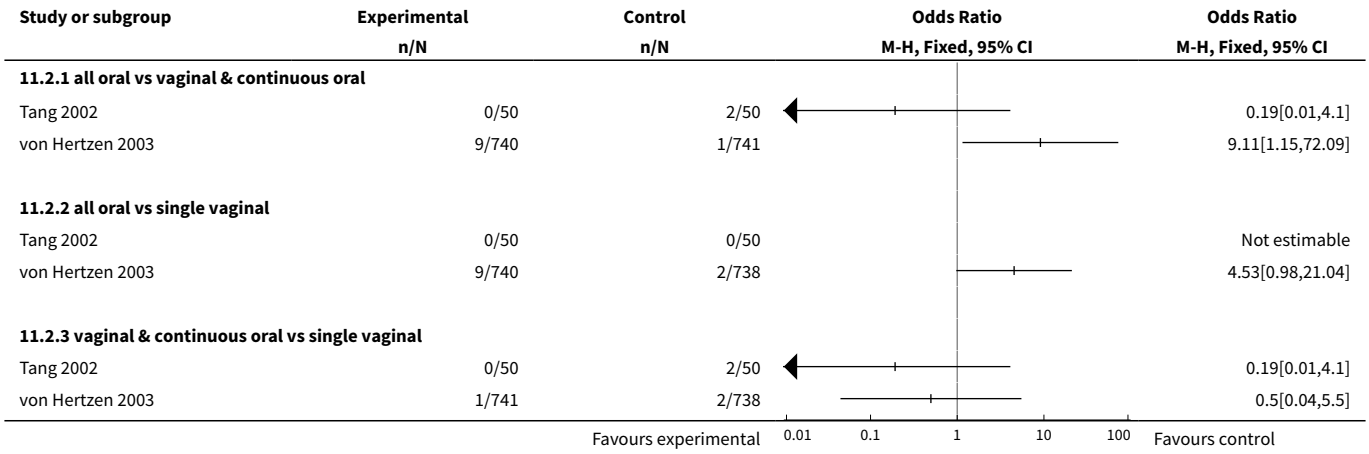
Analysis 11.1. Comparison 11 combined regimen mifepristone/prostaglandin:single vs continuous prostaglandin, Outcome 1 failure to achieve complete abortion.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
11.1.1 all oral vs vaginal & continuous oral					
Tang 2002	5/50	3/50		7.15%	1.67[0.42,6.6]
von Hertzen 2003	57/740	39/741		92.85%	1.46[0.99,2.17]
Subtotal (95% CI)	**790**	**791**		**100%**	**1.48[1.01,2.16]**
Total events: 62 (Experimental), 42 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.86); I^2=0%					
Test for overall effect: Z=2.02(P=0.04)					
11.1.2 all oral vs single vaginal					
Tang 2002	5/50	4/50		7.68%	1.25[0.36,4.38]
von Hertzen 2003	57/740	48/738		92.32%	1.18[0.82,1.71]
Subtotal (95% CI)	**790**	**788**		**100%**	**1.19[0.83,1.7]**
Total events: 62 (Experimental), 52 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.94); I^2=0%					
Test for overall effect: Z=0.96(P=0.34)					
11.1.3 vaginal & continuous oral vs single vaginal					
Tang 2002	3/50	4/50		7.68%	0.75[0.18,3.18]
von Hertzen 2003	39/741	48/738		92.32%	0.81[0.54,1.22]
Subtotal (95% CI)	**791**	**788**		**100%**	**0.8[0.54,1.19]**
Total events: 42 (Experimental), 52 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=1.08(P=0.28)					
11.1.4 all oral vs vaginal & continuous oral </=49 days					
von Hertzen 2003	15/236	13/240		100%	1.17[0.57,2.41]
Subtotal (95% CI)	**236**	**240**		**100%**	**1.17[0.57,2.41]**
Total events: 15 (Experimental), 13 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.43(P=0.66)					
11.1.5 all oral vs vaginal & continuous oral > 49 days					
von Hertzen 2003	42/504	26/500		100%	1.6[1,2.57]
Subtotal (95% CI)	**504**	**500**		**100%**	**1.6[1,2.57]**
Total events: 42 (Experimental), 26 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.95(P=0.05)					
11.1.6 all oral vs single vaginal >/=49 days					
von Hertzen 2003	15/236	11/223		100%	1.29[0.6,2.74]
Subtotal (95% CI)	**236**	**223**		**100%**	**1.29[0.6,2.74]**
Total events: 15 (Experimental), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					
11.1.7 all oral vs single vaginal > 49 days					
von Hertzen 2003	42/504	38/510		100%	1.12[0.73,1.7]
Subtotal (95% CI)	**504**	**510**		**100%**	**1.12[0.73,1.7]**
Total events: 42 (Experimental), 38 (Control)					

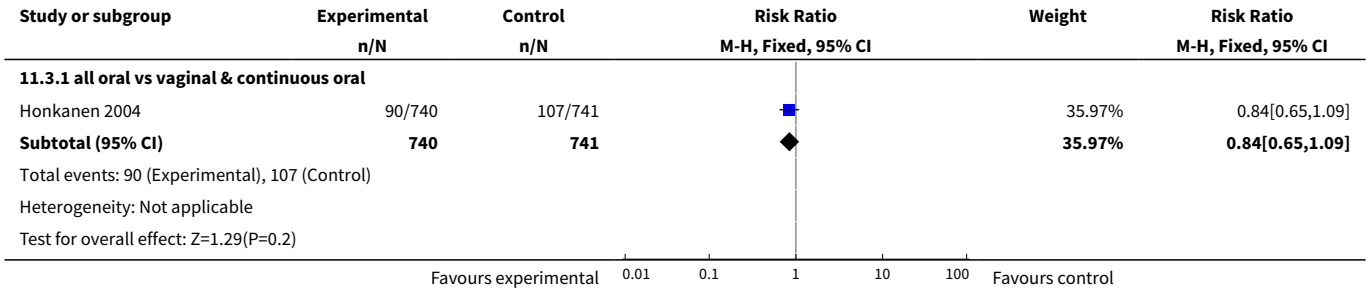


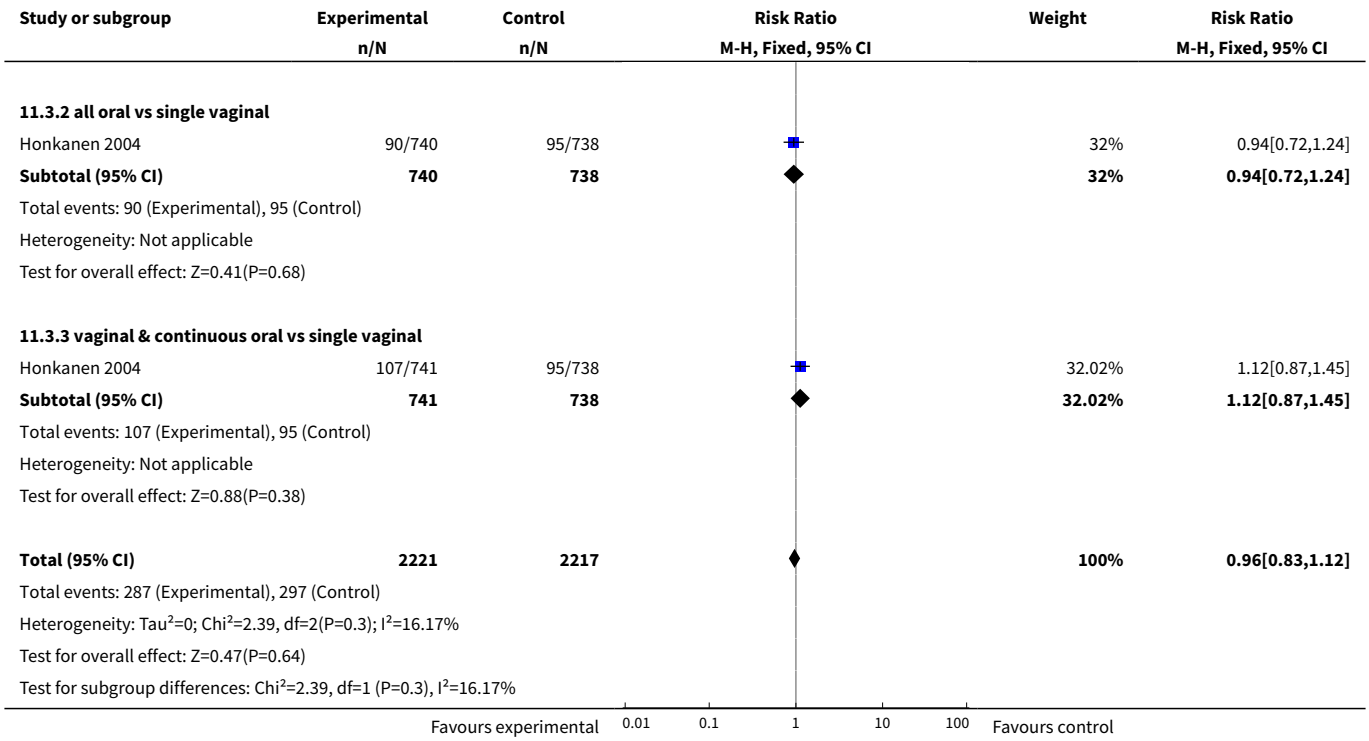


Analysis 11.2. Comparison 11 combined regimen mifepristone/prostaglandin:single vs continuous prostaglandin, Outcome 2 ongoing pregnancy at follow-up.

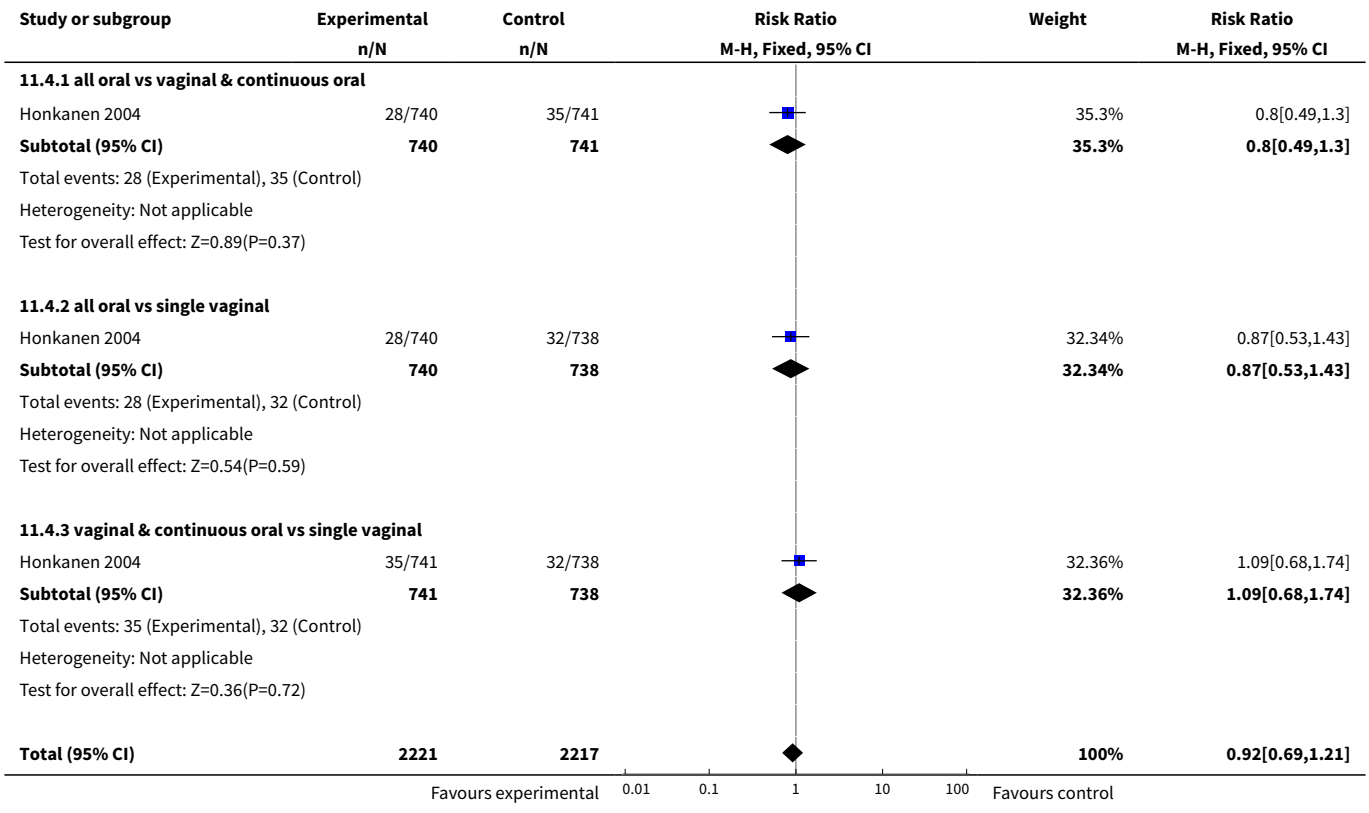


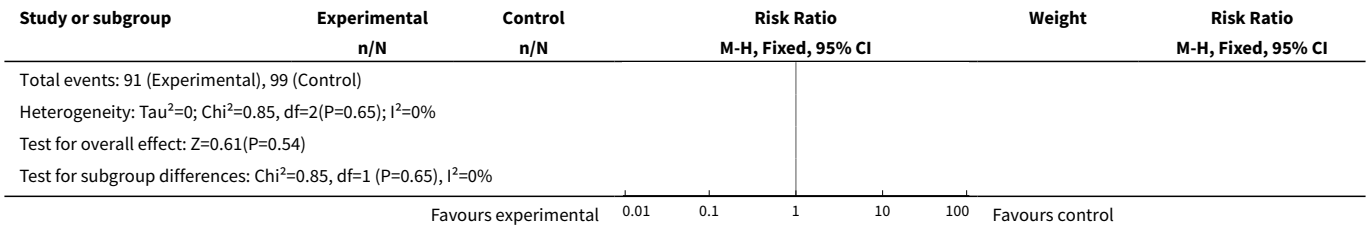
Analysis 11.3. Comparison 11 combined regimen mifepristone/ prostaglandin:single vs continuous prostaglandin, Outcome 3 nausea.



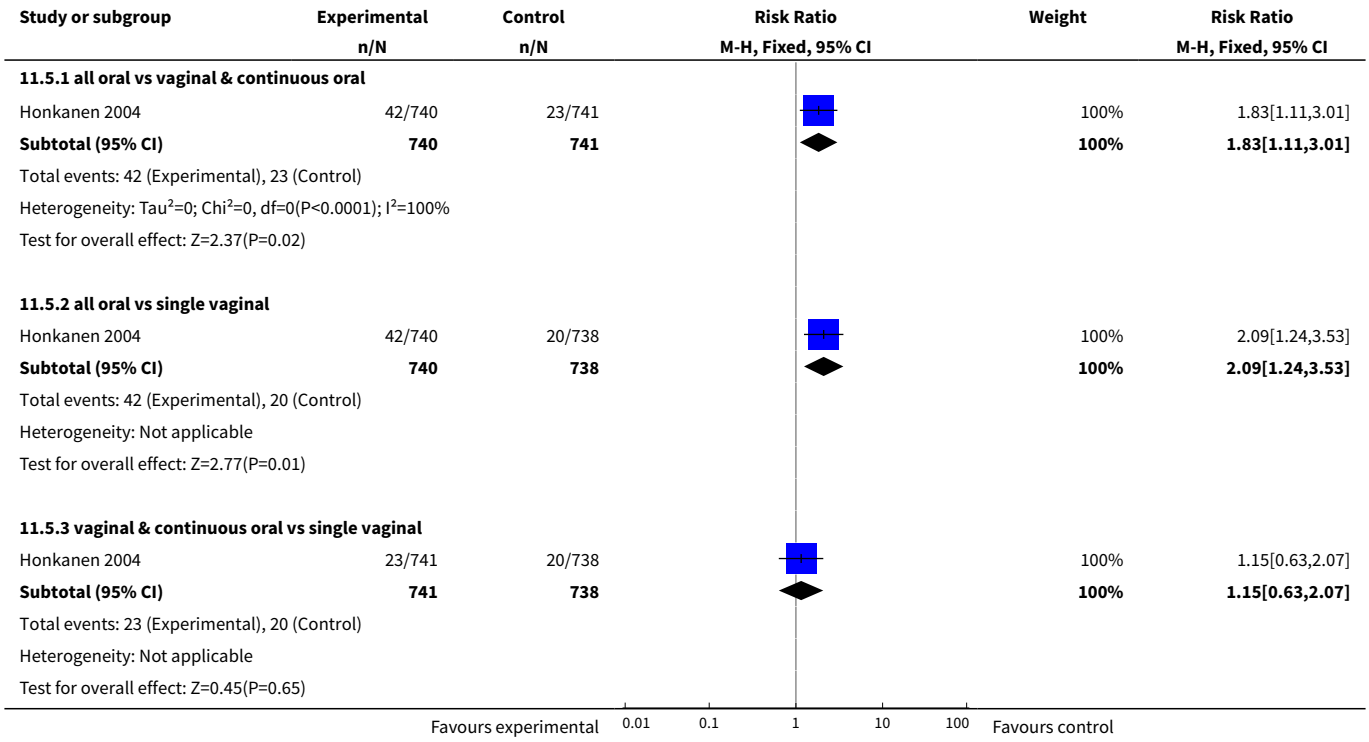


Analysis 11.4. Comparison 11 combined regimen mifepristone/ prostaglandin:single vs continuous prostaglandin, Outcome 4 vomiting.





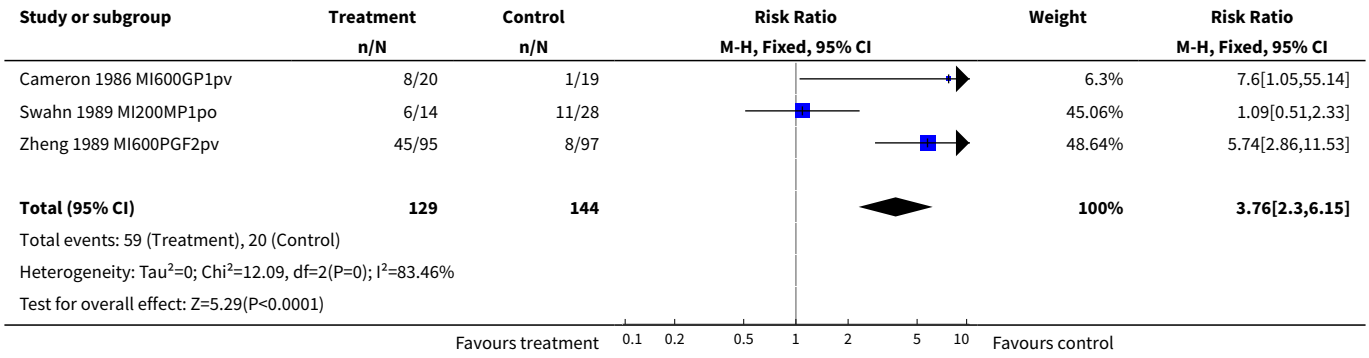
Analysis 11.5. Comparison 11 combined regimen mifepristone/ prostaglandin:single vs continuous prostaglandin, Outcome 5 diarrhoea.



Comparison 12. mifepristone alone vs combined regimen mifepristone/prostaglandin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	3	273	Risk Ratio (M-H, Fixed, 95% CI)	3.76 [2.30, 6.15]

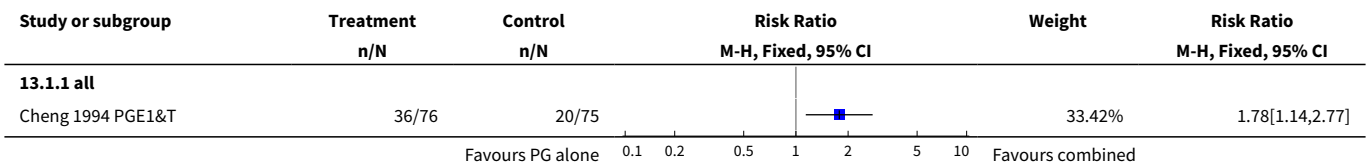
Analysis 12.1. Comparison 12 mifepristone alone vs combined regimen mifepristone/prostaglandin, Outcome 1 failure to achieve complete abortion.

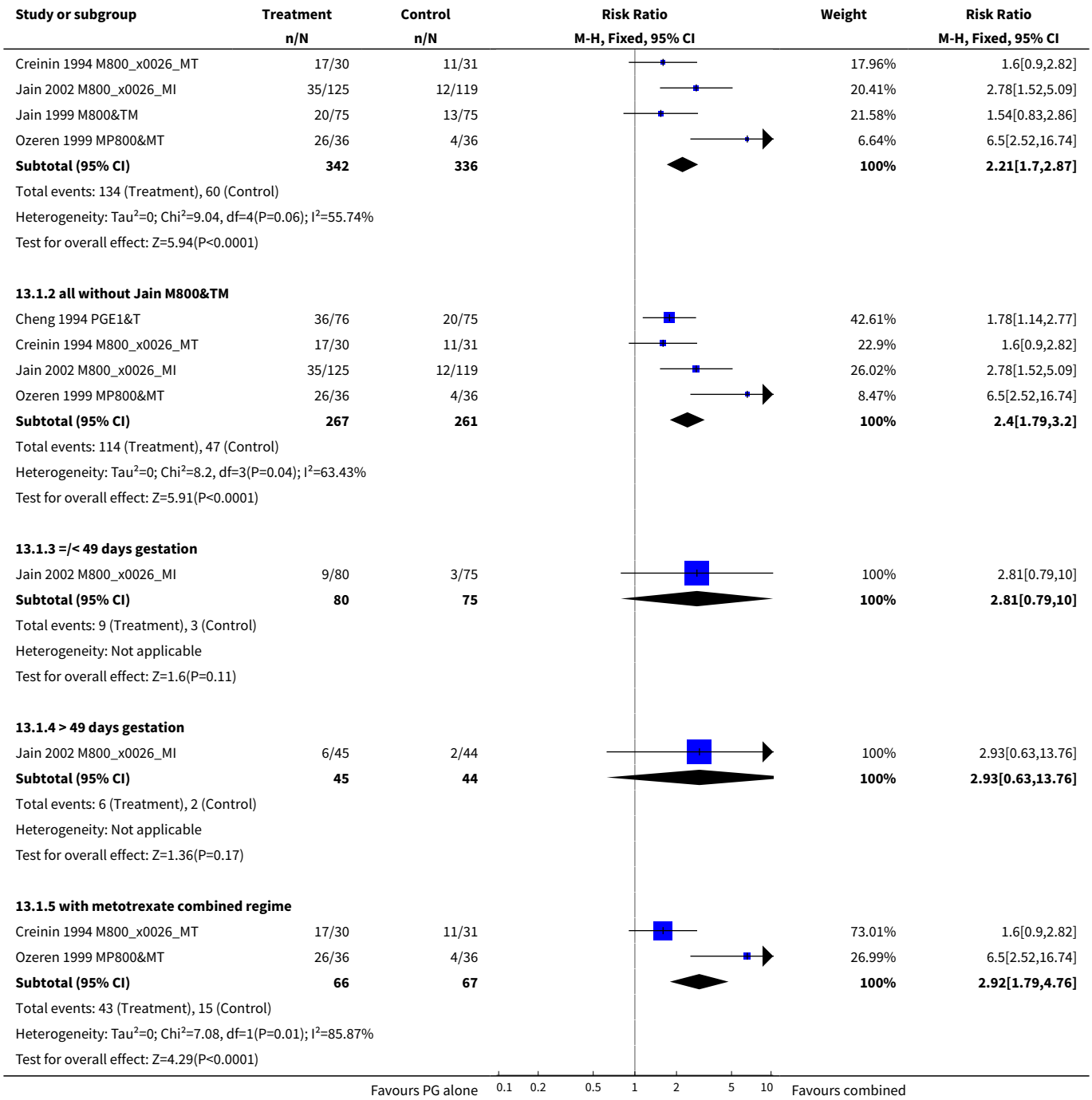


Comparison 13. prostaglandin alone vs combined regimen (all)

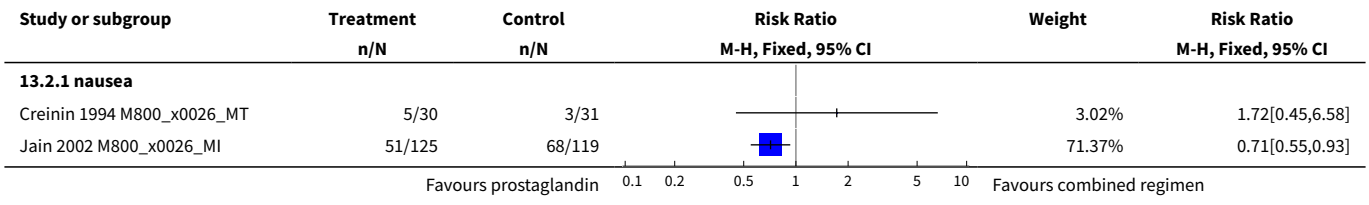
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 all	5	678	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [1.70, 2.87]
1.2 all without Jain M800&TM	4	528	Risk Ratio (M-H, Fixed, 95% CI)	2.40 [1.79, 3.20]
1.3 =/< 49 days gestation	1	155	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [0.79, 10.00]
1.4 > 49 days gestation	1	89	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.63, 13.76]
1.5 with metotrexate combined regime	2	133	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [1.79, 4.76]
2 side effects	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 nausea	3	377	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.56, 0.88]
2.2 vomiting	3	466	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 1.00]
2.3 diarrhoea	4	527	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.95, 1.59]

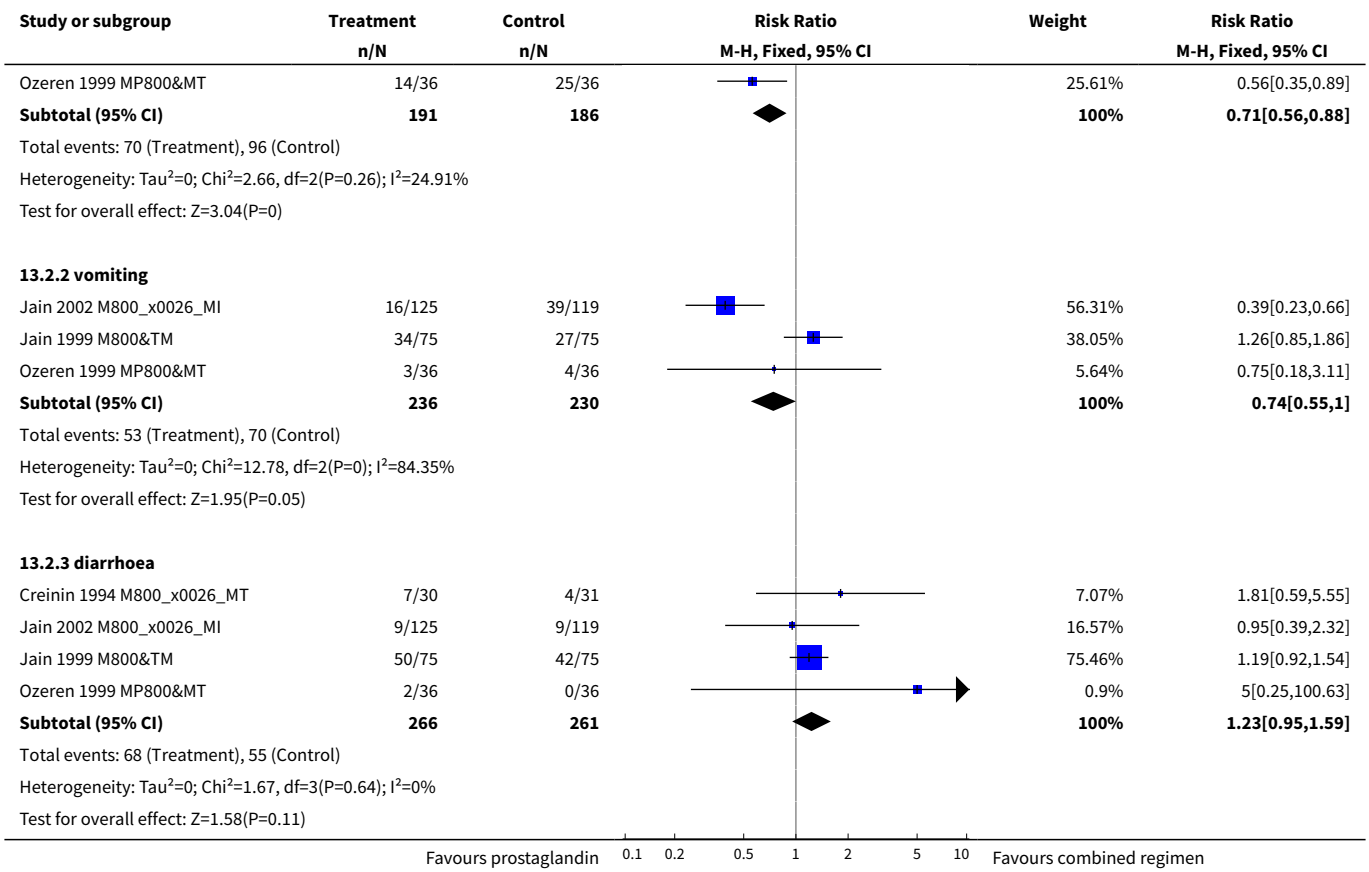
Analysis 13.1. Comparison 13 prostaglandin alone vs combined regimen (all), Outcome 1 failure to achieve complete abortion.





Analysis 13.2. Comparison 13 prostaglandin alone vs combined regimen (all), Outcome 2 side effects.

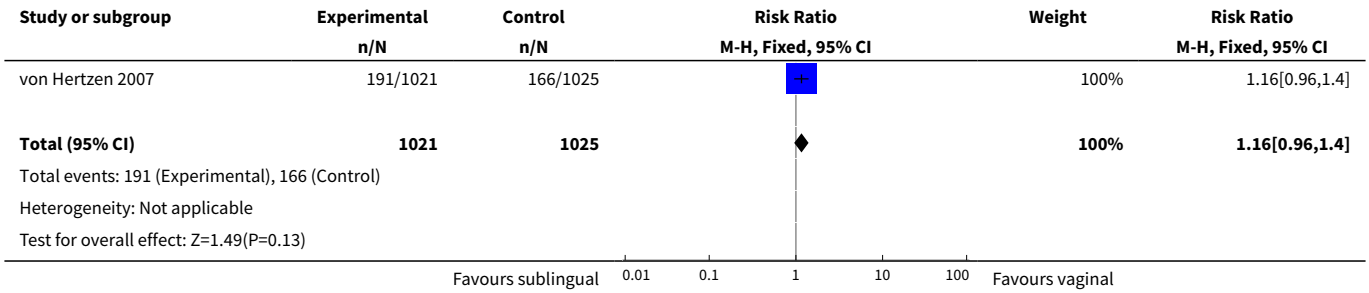




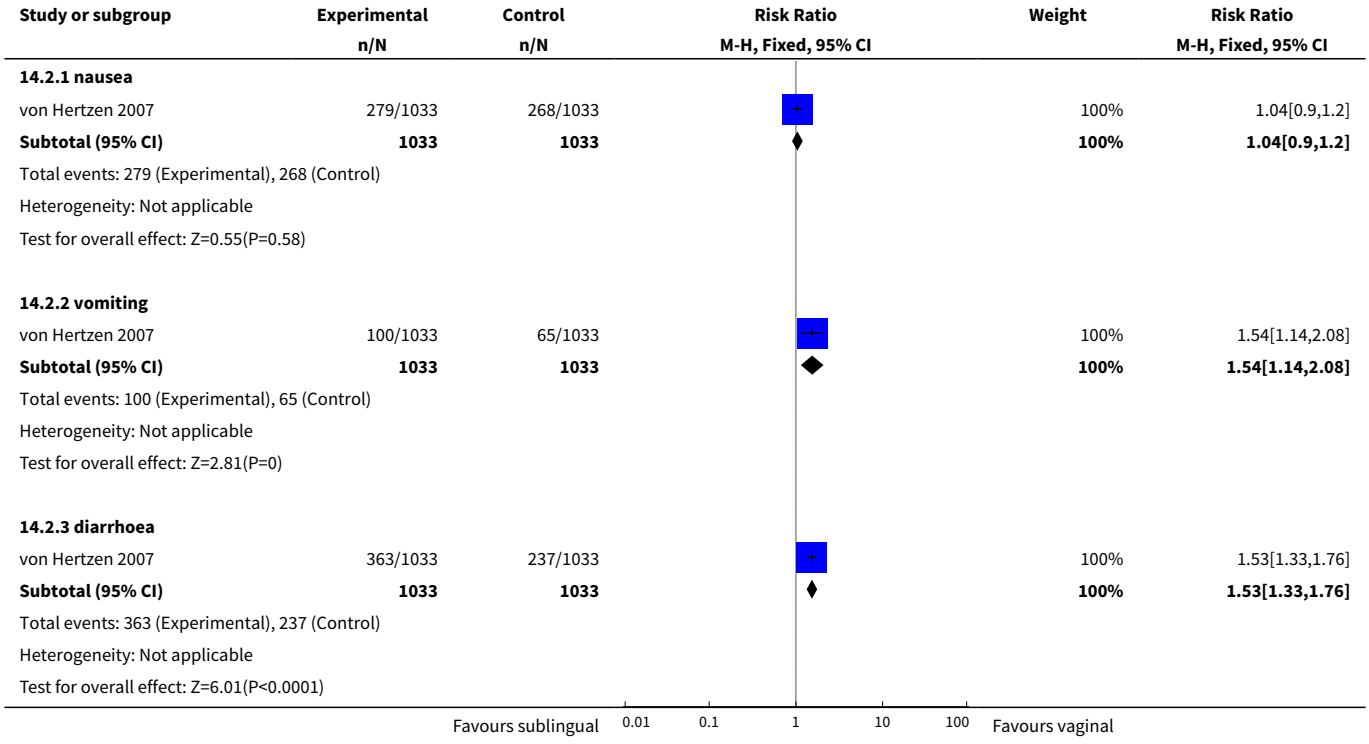
Comparison 14. prostaglandin alone: route of administration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1	2046	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.96, 1.40]
2 side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 nausea	1	2066	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.20]
2.2 vomiting	1	2066	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.14, 2.08]
2.3 diarrhoea	1	2066	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.33, 1.76]

Analysis 14.1. Comparison 14 prostaglandin alone: route of administration, Outcome 1 failure to achieve complete abortion.



Analysis 14.2. Comparison 14 prostaglandin alone: route of administration, Outcome 2 side effects.

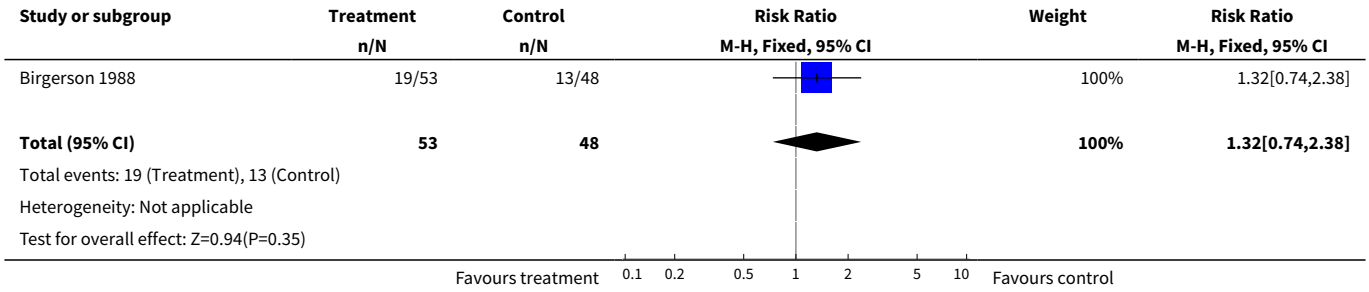


Comparison 15. mifepristone single - high vs low dose

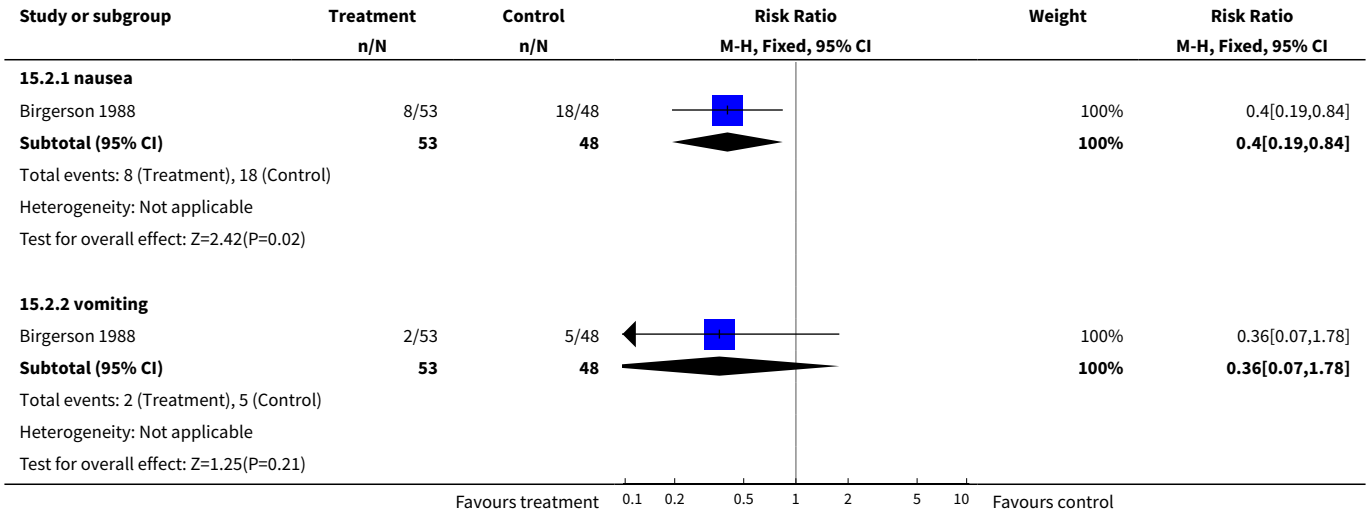
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.74, 2.38]
2 side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 nausea	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.19, 0.84]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.2 vomiting	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.07, 1.78]

Analysis 15.1. Comparison 15 mifepristone single - high vs low dose, Outcome 1 failure to achieve complete abortion.



Analysis 15.2. Comparison 15 mifepristone single - high vs low dose, Outcome 2 side effects.

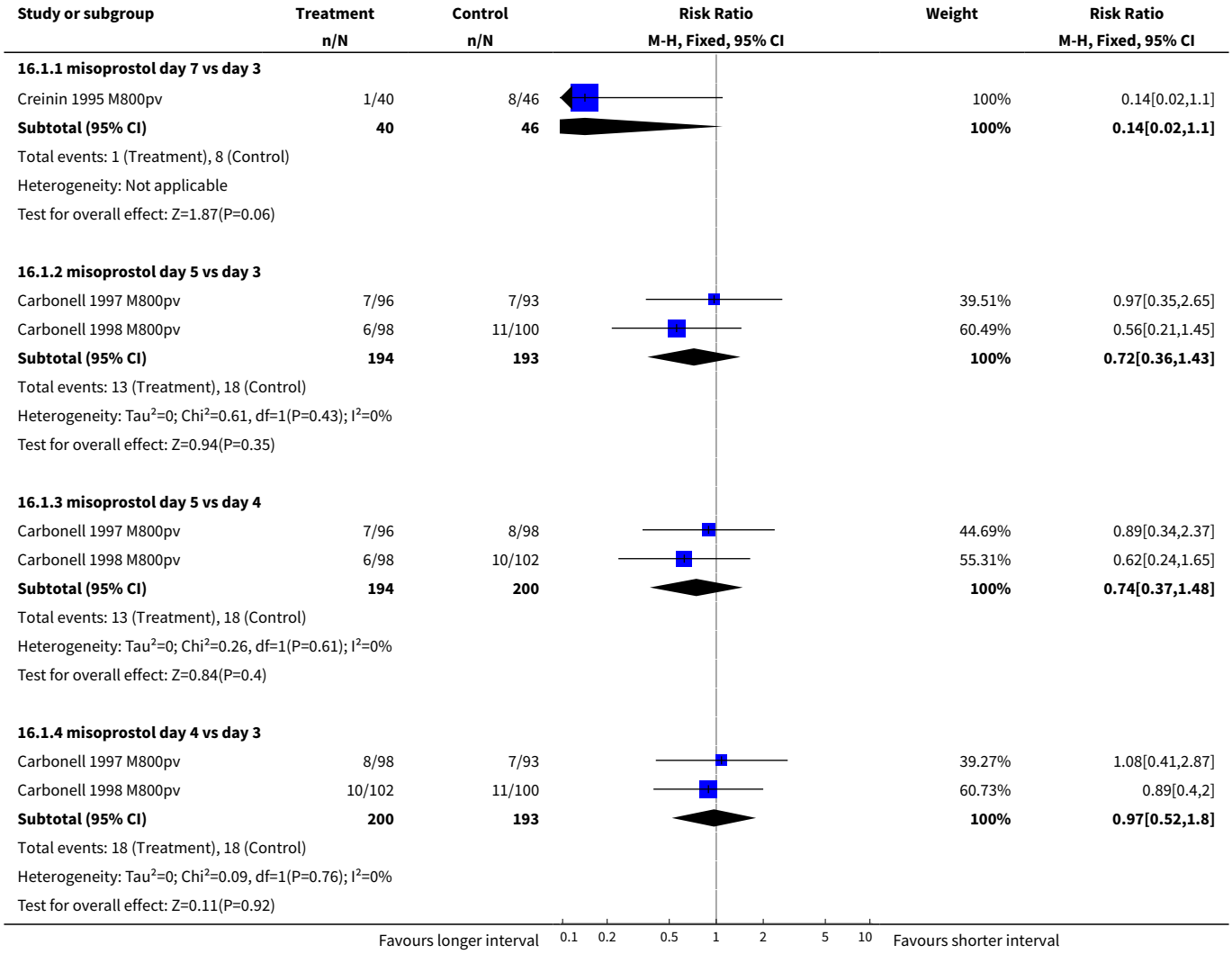


Comparison 16. combined regimen methotrexate/prostaglandin: timing of prostaglandin

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 failure to achieve complete abortion	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 misoprostol day 7 vs day 3	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.10]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.2 misoprostol day 5 vs day 3	2	387	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.36, 1.43]
1.3 misoprostol day 5 vs day 4	2	394	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.37, 1.48]
1.4 misoprostol day 4 vs day 3	2	393	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.52, 1.80]

Analysis 16.1. Comparison 16 combined regimen methotrexate/prostaglandin: timing of prostaglandin, Outcome 1 failure to achieve complete abortion.

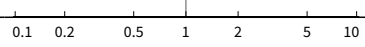


Comparison 17. combined regimen methotrexate/prostaglandin: methotrexate imi vs po

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1	100	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.51, 8.07]
2 Side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 nausea	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.22, 1.25]
2.2 vomiting	1	100	Risk Ratio (M-H, Fixed, 95% CI)	4.89 [0.57, 42.21]
2.3 diarrhoea	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.18, 8.34]

Analysis 17.1. Comparison 17 combined regimen methotrexate/prostaglandin: methotrexate imi vs po, Outcome 1 failure to achieve complete abortion.

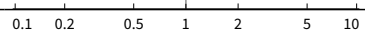
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Wiebe 1999 B	5/45	3/55		100%	2.04[0.51,8.07]
Total (95% CI)	**45**	**55**		**100%**	**2.04[0.51,8.07]**
Total events: 5 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.01(P=0.31)					



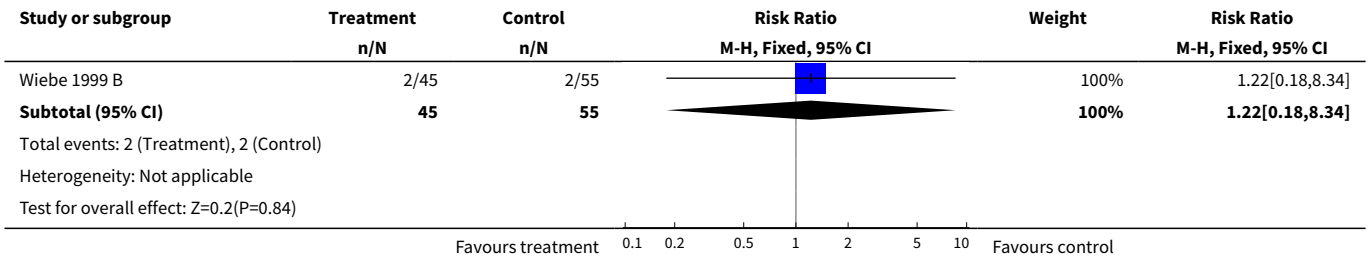
Favours treatment — Favours control

Analysis 17.2. Comparison 17 combined regimen methotrexate/prostaglandin: methotrexate imi vs po, Outcome 2 Side effects.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
17.2.1 nausea					
Wiebe 1999 B	6/45	14/55		100%	0.52[0.22,1.25]
Subtotal (95% CI)	**45**	**55**		**100%**	**0.52[0.22,1.25]**
Total events: 6 (Treatment), 14 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.45(P=0.15)					
17.2.2 vomiting					
Wiebe 1999 B	4/45	1/55		100%	4.89[0.57,42.21]
Subtotal (95% CI)	**45**	**55**		**100%**	**4.89[0.57,42.21]**
Total events: 4 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.44(P=0.15)					
17.2.3 diarrhoea					



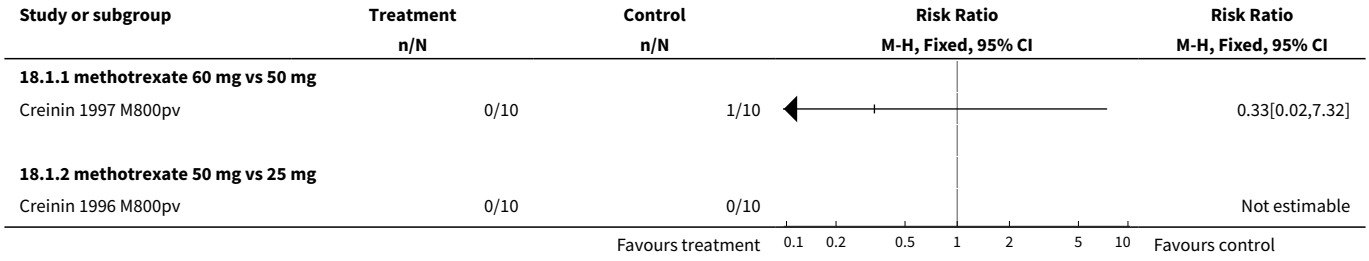
Favours treatment — Favours control



Comparison 18. combined regimen methotrexate/prostaglandin: dose of methotrexate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 methotrexate 60 mg vs 50 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 methotrexate 50 mg vs 25 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 18.1. Comparison 18 combined regimen methotrexate/prostaglandin: dose of methotrexate, Outcome 1 failure to achieve complete abortion.



Comparison 19. combined regimen methotrexate/prostaglandin: route of prostaglandin (misoprostol)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 nausea	1	309	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.84, 1.42]
2.2 vomiting	1	309	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.67, 1.56]

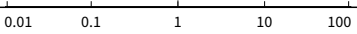
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.3 diarrhoea	1	309	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.94, 2.07]

Analysis 19.1. Comparison 19 combined regimen methotrexate/prostaglandin: route of prostaglandin (misoprostol), Outcome 1 failure to achieve complete abortion.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Wiebe 2004	72/155	50/154		0%	1.43[1.08,1.9]

Analysis 19.2. Comparison 19 combined regimen methotrexate/ prostaglandin: route of prostaglandin (misoprostol), Outcome 2 side effects.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
19.2.1 nausea					
Wiebe 2004	68/155	62/154		100%	1.09[0.84,1.42]
Subtotal (95% CI)	**155**	**154**		**100%**	**1.09[0.84,1.42]**
Total events: 68 (Experimental), 62 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
19.2.2 vomiting					
Wiebe 2004	34/155	33/154		100%	1.02[0.67,1.56]
Subtotal (95% CI)	**155**	**154**		**100%**	**1.02[0.67,1.56]**
Total events: 34 (Experimental), 33 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.11(P=0.91)					
19.2.3 diarrhoea					
Wiebe 2004	45/155	32/154		100%	1.4[0.94,2.07]
Subtotal (95% CI)	**155**	**154**		**100%**	**1.4[0.94,2.07]**
Total events: 45 (Experimental), 32 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.66(P=0.1)					

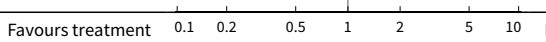


Comparison 20. tamoxifen vs methotrexate (combined with prostaglandin) : low dose tamoxifen (40)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1	198	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.86, 4.84]
2 side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 nausea	1	198	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.33, 0.97]
2.2 vomiting	1	198	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.42, 6.92]
2.3 diarrhoea	1	198	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.26, 8.96]

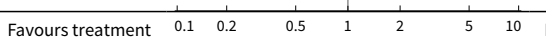
Analysis 20.1. Comparison 20 tamoxifen vs methotrexate (combined with prostaglandin) : low dose tamoxifen (40), Outcome 1 failure to achieve complete abortion.

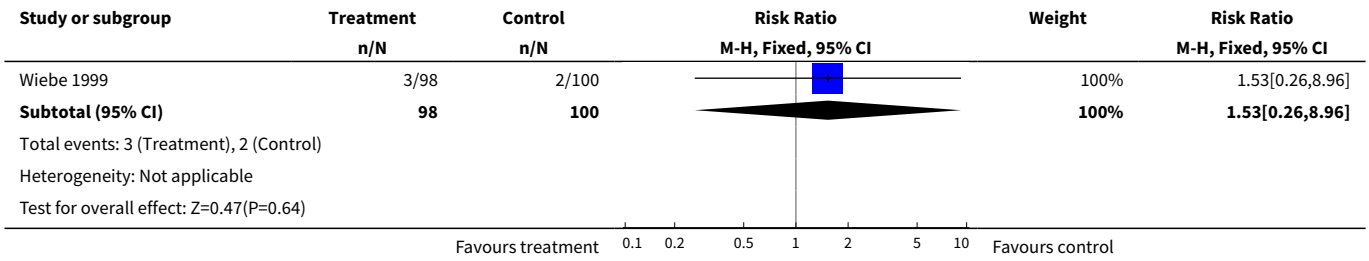
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Wiebe 1999	14/98	7/100		100%	2.04[0.86,4.84]
Total (95% CI)	**98**	**100**		**100%**	**2.04[0.86,4.84]**
Total events: 14 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.62(P=0.11)					



Analysis 20.2. Comparison 20 tamoxifen vs methotrexate (combined with prostaglandin) : low dose tamoxifen (40), Outcome 2 side effects.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
20.2.1 nausea					
Wiebe 1999	16/98	29/100		100%	0.56[0.33,0.97]
Subtotal (95% CI)	**98**	**100**		**100%**	**0.56[0.33,0.97]**
Total events: 16 (Treatment), 29 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.07(P=0.04)					
20.2.2 vomiting					
Wiebe 1999	5/98	3/100		100%	1.7[0.42,6.92]
Subtotal (95% CI)	**98**	**100**		**100%**	**1.7[0.42,6.92]**
Total events: 5 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.74(P=0.46)					
20.2.3 diarrhoea					

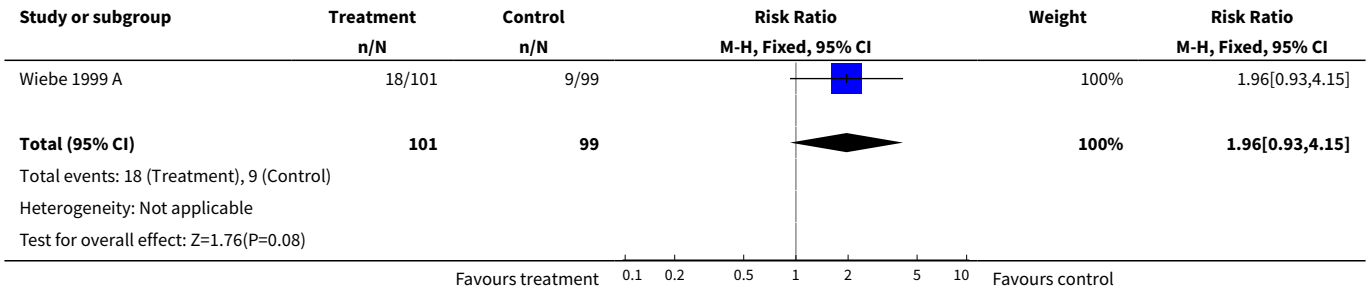




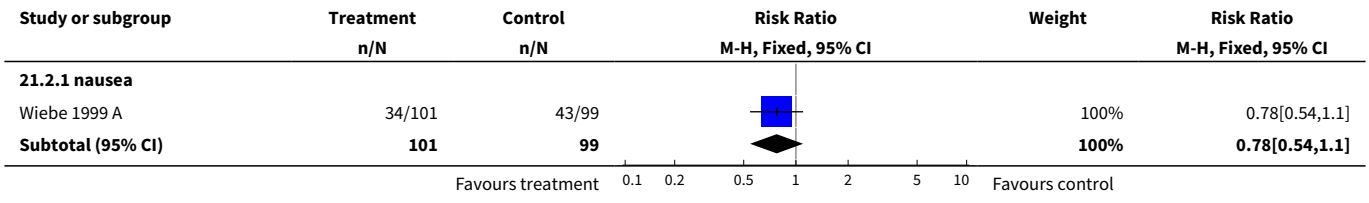
Comparison 21. tamoxifen vs methotrexate (combined with prostaglandin): high dose tamoxifen (160 mg)

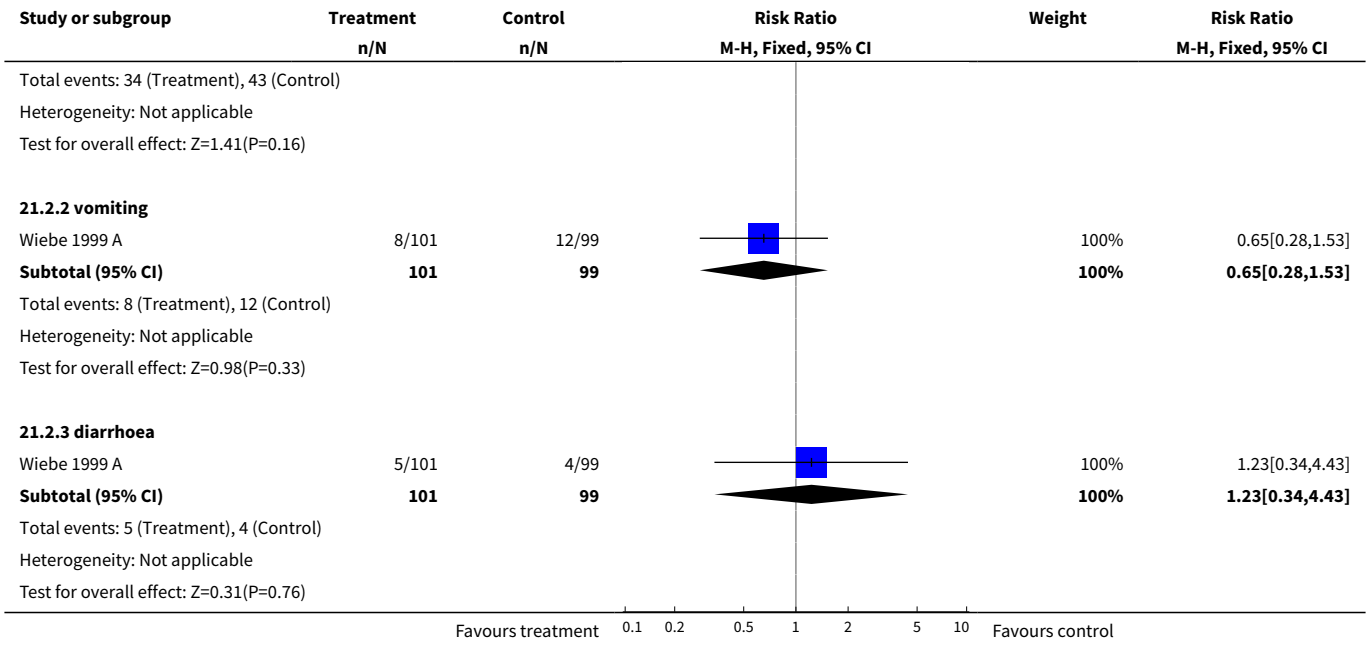
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [0.93, 4.15]
2 side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 nausea	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.54, 1.10]
2.2 vomiting	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.28, 1.53]
2.3 diarrhoea	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.34, 4.43]

Analysis 21.1. Comparison 21 tamoxifen vs methotrexate (combined with prostaglandin): high dose tamoxifen (160 mg), Outcome 1 failure to achieve complete abortion.



Analysis 21.2. Comparison 21 tamoxifen vs methotrexate (combined with prostaglandin): high dose tamoxifen (160 mg), Outcome 2 side effects.

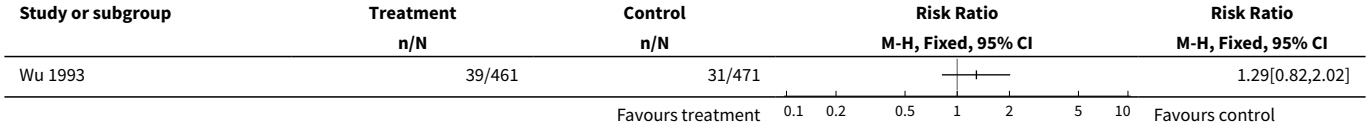




Comparison 22. combined regimen mifepristone/prostaglandin vs mifepristone/prostaglandin and tamoxifen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 failure to achieve complete abortion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 22.1. Comparison 22 combined regimen mifepristone/prostaglandin vs mifepristone/prostaglandin and tamoxifen, Outcome 1 failure to achieve complete abortion.



ADDITIONAL TABLES

Table 1. other studies included in the review

Study	Intervention	Outcomes
Wang 2000	Group 1: Day 1: mifepristone 50mg/po 12hourly /2 doses),day 2-7: mifepristone 25mg po/day Day 3: misoprostol 600mcg/po, day 4-6: misoporstol 200mcg/day	failure to achieve complete abortion: group 1: 18/1118 group 2: 59/494

Table 1. other studies included in the review *(Continued)*

	Group 2: Day 1: mifepristone 50mg, followed by 25mg/12hourly/4 times Day 3: misoprostol 600mcg/po	ongoing pregnancy: group1:2/1118 group2: 6/494
Arvidsson 2005	Day 1: both groups receive mifepristone 600mg Day 3: group 1: misprostol 400mcg/po group 2: 800mcg/pv	nausea: group1: 23/48 group2: 17/49 vomiting: group1: 11/48 group2: 5/49 diarrhoea: group1: 3/48 group2: 1/49 women dissatisfied with procedure: group1: 2/48 group2: 1/49
Wiebe 2006	Group 1: methotrexate 50 mg/ m2 followed >/ 72 hours by 400mcg misoprostol vaginal Group 2: misoprostol 400mcg sublingual AND 400mcg misoprostol vaginal	failure to achieve complete abortion: group1: 62/149 group2: 57/149 nausea: group1: 53/49 group2: 54/149 vomiting: group1: 17/149 group2: 21/149 diarrhoea: group1: 16/149 group2: 41/149 surgical abortion: group1: 9/149 group2: 18/149
Liao 2004	Group 1: mifepristone given: 50 mg, then 12 hrs later 25 mg, then 12 hrs later 50 mg, and finally, 12 hrs later, 25 mg mifepristone. 24 hrs after, 600 mcg misoprostol oral (total: 150mg) Group 2: mifepristone given 30 mg, then 15 mg every 12 hours for 3 doses. 24 hrs after last dose, 600 mcg misoprostol given oral. (total: 75 mg)	failure to achieve complete abortion: group1: 11/240 group2: 9/240 ongoing pregnancy: group1: 2/240 group2: 1/240

Table 1. other studies included in the review *(Continued)*

WHO 1989	Group 1: mifepristone 25mg/twice daily for 3 days (total 150 mg) and sulprostone0.25 mg /intramuscular/ on third day a.m. Group 2: mifepristone 25mg /twice daily for 4 days (total 200mg) and sulprostone0.25 mg /intramuscular/ on fourth day a.m.	failure to achieve complete abortion: group1: 15/125 group2: 13/126 ongoing pregnancy: group1: 3/125 group2: 3/126
WHO 1991	Group 1: mifepristone 25mg/12 hourly/ 5 doses (total 125mg) and gemeprost 1mg/vaginally 60 hours after the start of the treatment Group 2: mifepristone 600mg/single dose and gemeprost 1mg/vaginally 60 hours after the start of the treatment	failure to achieve complete abortion: group1: 12/181 group2: 15/187

WHAT'S NEW

Date	Event	Description
3 October 2011	New citation required but conclusions have not changed	New author Nathalie Kapp helped updating this review and 19 new studies were added

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 1, 2004

Date	Event	Description
15 April 2008	Amended	Converted to new review format.
17 October 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

RK had the idea and wrote the review. RK and NK did the data extraction. NK, AMG, GJH, CLN and AC reviewed and contributed substantially in all aspects of the review.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Effective Care Research Unit, University of the Witwatersrand, South Africa.
- HRP- UNDP/UNFPA/WHO/WORLD BANK Special Programme in Human Reproduction, Geneva, Switzerland.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Abortifacient Agents [administration & dosage]; Abortion, Incomplete [chemically induced]; Abortion, Induced [adverse effects] [*methods]; Drug Therapy, Combination; Methotrexate [administration & dosage]; Mifepristone [administration & dosage]; Misoprostol [administration & dosage]; Pregnancy Trimester, First; Prostaglandins [administration & dosage]; Randomized Controlled Trials as Topic; Tamoxifen [administration & dosage]

MeSH check words

Female; Humans; Pregnancy