Medical methods for first trimester abortion (Review)

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ABSTRACT

Background
Surgical abortion up to 63 days by vacuum aspiration or dilatation and curettage has been the method of choice 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 strategy
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 (e.g. single drug, combination), ways of application, or different dose regimens, single or combined, for medical abortion, were considered. Trials were assessed and included if they had adequate concealment of allocation, randomisation procedure and follow-up. Women, pregnant in the first trimester, undergoing medical abortion were the participants. Different medical methods used for first trimester abortion, compared with each other or placebo were included. The outcomes sought include mortality, 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, diarrhoea.

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. A form was designed to facilitate the data extraction. Data were processed using Revman software.

Main results
Thirty-nine 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. 2) Mifepristone alone is less effective compared to the combined regimen mifepristone/ prostaglandin (RR 3.76 95% CI 2.30 to 6.15). 3) Similarly, the 5 trials included in the comparison of prostaglandin compared to the combined regimen reported in all but one higher effectiveness with the combined regime compared to prostaglandin. The results of

these studies were not pooled but the RR of failure with prostaglandin alone is between 1.4 to 3.75 and the 95% confidence intervals indicate 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 when using split dose compared to single dose of prostaglandin. 6) Combined regimen methotrexate/prostaglandin: there was no statistically significant difference in failure to achieve complete abortion comparing methotrexate administered intramuscular to oral (RR 2.04, 95% CI 0.51 to 8.07). Similarly, early (day 3) vs late (day 5) administration of prostaglandin showed no significant difference (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. Misoprostol vaginally is more effective than orally. Some of the results are based on small studies only and therefore carry some uncertainty. Almost all trials were conducted in hospital settings with good access to support and emergency services. It is therefore not clear if the results are readily applicable to under-resourced settings where such services are lacking even if the agents used are available.

PLAIN LANGUAGE SUMMARY

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

There are several different surgical techniques for early termination of pregnancy (abortion in 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. The 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 hospitals where women returned for check-up.

BACKGROUND

Up to 53 million abortions are performed each year (WHO 1997). An estimated one-third are performed under unsafe conditions. Medical abortion has the potential to be provided in the community by nursing staff and be lower in cost compared to surgical methods.

Surgical abortion up to 63 days by vacuum aspiration or dilatation and curettage has been the method of choice 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. Large uncontrolled studies suggest that early medical abortion with mifepristone and a prostaglandin seems to be an effective method for pregnancy termination (Urquhart 1997).

Various drugs have been used for first trimester abortion. The most widely researched ones 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 termination of pregnancy. The most commonly used prostaglandins are gemeprost given vaginally and misoprostol, either oral or vaginal. Misoprostol is a prostaglandin analogue registered for use in non-steroidal 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). The reported complete abortion rate for misoprostol alone varies between 61% for single and 93% for repeat doses (Bugalho 1996, Carbonell 1997). Gemeprost used alone was less effective to induce complete abortion than in combination with mifepristone (Norman 1992).

Mifepristone as an antiprogestogen blocks the receptors for progesterones and glucocorticosteroids 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 since 1991 and in Sweden since 1992. Mifepristone given alone has been shown to lead only in 60-80% of cases to abortion, depending on the gestational age and the dose given (WHO 1997). However, the combination with a prostaglandin at up to 63 days of amenorrhoea leads to complete abortion in about 95% of pregnancies (United Kingdom 1990). The effect of mifepristone develops over a time period of 24-48 hours. Therefore

prostaglandins are usually administered after 36-48 hours. The optimal dose of mifepristone as well as of misoprostol is not known and different regimens are in use. The recommended regimen by the manufacturer is mifepristone 600 mg followed by misoprostol (betweeen 400 - 800 mcg, orally or vaginally) or gemeprost (0.5 - 1 mg vaginally) and is used 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 may have 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).

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). Compared to surgical procedures the observed blood loss is greater (Winikoff 1997).

Failed abortion is an infrequent but important complication of medical methods. Both methotrexate and misoprostol may lead to fetal anomalies if the pregnancy persists (Grimes 1997).

Some data suggest that more women choose medical rather than surgical abortion. ' More natural', 'being easier', more private', and 'can be done earlier in pregnancy' were reasons to opt for a medical method (Creinin 1996). Characteristics such as newness, less invasiveness, the possibility of verifying the expulsion and the naturalness of the method were reported by others (Bachelot 1992).

Medical methods for first trimester abortion are widely available in some countries but not available in many. Nevertheless, the number of countries introducing medical abortion methods increases steadily. It is therefore important to identify the best available agents and regimen for use. Comparison of medical methods with surgical evacuation is the subject of another review [Say 2003].

OBJECTIVES

To compare different medical methods for first trimester abortion.

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 assessed and included if they had adequate concealment of allocation, randomisation procedure and follow-up.

Types of participants

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

Types of intervention

Different medical methods used for first trimester abortion, compared with each other or placebo. See 'search strategy' 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, diarrhoea. Although mortality is considered an important outcome we did not anticipate addressing abortion-related mortality within the context of these trials.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

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.

METHODS OF THE REVIEW

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), mean duration of days of bleeding. A further division into early (=/< 49 days of amenorrhoea) and late (> 49 days) 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 the trials included in the meta-analysis: GP -gemeprost, the number next to it - refers to the dose of gemeprost in gram, 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.

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. 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 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 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: time of prostaglandin (comparison 4)
- Intervention: misoprostol orally versus vaginally (comparison 5)
- Intervention:single versus split dose prostaglandin (comparison 6)
- Mifepristone single dose versus combined regimen mifepristone/prostaglandin (comparison 7)
- Prostaglandin alone versus a combined regimen (all) (comparison 8)
- Mifepristone single regimen - high versus low dose (comparison 9)

Combined regimen methotrexate/prostaglandin:

- Intervention: timing of prostaglandin (comparison 10)
- Intervention: route of methotrexate: intramuscular versus orally (comparison 11)
- Intervention: dose of methotrexate (comparison 12)

Tamoxifen versus methotrexate (combined with prostaglandin):

- Intervention: low dose tamoxifen (40 mg)(comparison 13)
- Intervention:high dose tamoxifen (160 mg) (comparison 14)

Combined regimen mifepristone/prostaglandin versus mifepristone/prostaglandin and tamoxifen (comparison 15)

DESCRIPTION OF STUDIES

see table: characteristics of included studies

METHODOLOGICAL QUALITY

Twenty trials scored A and 19 trials scored B for concealment of allocation. Two trials used open-label design (Schaff 2000, Schaff 2001).

Two of the trials mentioned 'intention -to -treat analysis' (WHO M400po, WHO 01 GP1pv).

RESULTS

Thirty-nine trials are included in this review. Due to the many different interventions trials were grouped 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 mentioned and if so, they are included in the tables of included studies. Data are presented for different gestational ages where possible (= /< 49 days, > 49 days). One trial used 2 different comparisons, and is therefore listed as 2 different trials (Wiebe 1999 and Wiebe 1999 A).

Combined regimen mifepristone/prostaglandin

Intervention: dose of mifepristone: 600 versus 200 mg (comparison 1)

There are 7 (McKinley M600po; WHO 1989, WHO 1991, WHO 93 GP1pv, WHO M400po, WHO MI200/50, WHO 01GP1pv) trials included in the review, of which data from 4 trials with overall 3482 women were included in the meta-analysis (McKinley M600po; WHO 93 GP1pv, WHO M400pv, WHO 01GP1pv). There was no difference in effectiveness between 200 mg and 600 mg of mifepristone (RR 1.07 95% CI 0.87 - 1.32) with regard to the failure rate. There was no difference in nausea between the two groups (RR 1.05 95% CI 0.86-1.28) in the 2 trials included (WHO M400po, WHO 01 GP1pv). The remaining 3 trials compared other doses of mifepristone.

Combined regimen mifepristone/prostaglandin

Intervention: dose of prostaglandin (comparison 2)

Five trials are included in the review, the data from two of them could be included in the meta-analysis. These 2 trials (Rodger MI600, WHO 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 0.54-1.05). The largest trial in this comparison (WHO 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 is less significant (RR 0.81, 95% CI 0.45 - 1.43). The arm with the smallest dose (mifepristone 50 mg and gemeprost 0,5 mg) had to be stopped prematurely after 249 women were enrolled, as the effectiveness was below the predetermined cut-off point. Rodger (Rodger MI600) included 120 women in the study. However, the first 60 women were not randomised, therefore only data for the second 60 women are included in this review.

Combined regimen mifepristone/prostaglandin

Intervention: type of prostaglandin (comparison 3)

1)gemeprost versus misoprostol

Two trials are included (Baird GP0.5 M600po; Bartley GP0.5M800pv) using different doses of misoprostol and different route of administration. Therefore the results were not combined. However, when misoprostol is used at a higher dose (800 mcg) and vaginally it seems to be more effective compared to gemeprost 0.5 mg according to data from a single trial (RR 2.86 95%CI 1.14-7.18)(Bartley GP0.5M800pv) .

2)PGF2 alpha versus misoprostol

There was no difference when comparing PGF2 alpha to misoprostol 600 mcg orally (Sang 94 M600poPGF2pv, Sang 99 M600poPGF2pv)

Combined regimen mifepristone/prostaglandin

Intervention: time of prostaglandin (comparison 4)

The 3 trials included used different dose regimens as well as time intervals and the results are therefore presented for each trial separately. Misoprostol administered on day 3 seems to be less effective in achieving complete abortion when compared to day 1 (Schaff MI200M800). No difference regarding failure rate was shown in the individual trials when comparing day 3 versus day 2, day 2 versus day 1 and day 2 versus day 0 (Creinin MI600M400; Schaff 00 MI200M800, Sandstrom MI600GP1pv). There was no difference in the occurrence of side effects (nausea, vomiting, diarrhoea) in the 2 groups.

Combined regimen mifepristone/prostaglandin

Intervention : misoprostol orally versus vaginally (comparison 5)

Four trials are included in the review, 2 trials with a total of 1407 women are included in the meta-analysis (El-Refaey M800MI600; Schaff MI200M800). A statistically significant higher number of women had failure to achieve complete abortion when misoprostol was applied orally (RR 4.41 95% CI 2.32-8.38). Nausea and diarrhoea occurred more often in the group receiving misoprostol orally (RR 1.13 95% CI 1.02-1.25; RR 1.80 95% CI 1.49-2.18, respectively). Unexpectedly, vomiting occurred more often in the vaginal group and this result was based on one trial (Schaff M800MI200), and reporting error cannot be excluded. These data were not totalled. One trial used different doses orally and vaginally and was therefore not included in the meta-analysis (Creinin 2001). Tang (Tang 2002) used a combined regimen orally/vaginally in one group and was therefore not included in the meta-analysis.

Combined regimen: mifepristone/prostaglandin

Intervention: single versus split dose of prostaglandin (comparison 6)

One trial was included in this comparison (El Refaey 1994). There was no statistically or clinically significant difference between the 2 groups (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 in the 2 groups.

Mifepristone alone versus mifepristone/prostaglandin (comparison 7)

Three trials were included in this comparison: compared to the combination regimen, mifepristone alone was statistically

significantly less effective (RR of failure 3.76 95% CI 2.30 - 6.15) (Cameron MI600GP1pv, Swahn MI200MP1po, Zheng MI600PGF21pv).

Prostaglandin alone versus a combined regimen (all) (comparison 8)
Five trials were included in this comparison (Cheng PGE1&T; Creinin MP800&MT; Jain MP800&TM; Jain MP800&MI; Ozeren MP800&MT). Because different combined regimens were used in the trials, the results are not totalled but included in the meta-analysis graph for visual analysis. The studies consistently showed that compared to a combination regimen, misoprostol alone was statistically significantly less effective in achieving complete abortion. There was no statistically significant difference for side effects between the groups in the 2 trials reporting on it (nausea RR 0.68 95%CI 0.44 - 1.06; diarrhoea RR 2.17 95% CI 0.76 - 6-16) (Creinin MP800&MT; Ozeren MP800&MT)

Mifepristone single - high versus low dose (comparison 9)
One trial was included in this comparison (Birgerson 1988). No difference between low (140 mg) and high (700 mg) dose of mifepristone was found regarding the failure rate.

Combined regimen: methotrexate/prostaglandin
Timing of prostaglandin (comparison 10)
Three trials are included in the review (Carbonell 97 M800pv, Carbonell 98 M800pv, Creinin 95 M800pv) and data from 2 trials are included in the meta-analysis (Carbonell 97 M800pv; Carbonell 98 M800pv).There was no statistically significant difference of prostaglandin given on day 5 compared to day 3 (RR 0.72 95% CI 0.36-1.43) or day 5 to day 4 (RR 0.73 95% CI 0.37-1.48).

Route of methotrexate: intramuscular versus orally (comparison 11)
One trial compared intramuscular versus oral administration of methotrexate (Wiebe 1999 B). There was no difference regarding 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 12)
Two trials were eligible to be included in the review (Creinin 96 M800pv, Creinin 97 M800pv). Both trials had a very small sample size (10 women in each group); they used different dose regimens and are therefore presented separately.

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 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 13)
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 14)
There was no statistically significant difference regarding failure rates between the 2 groups (RR 1.96 95% CI 0.93-4.15) and 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 and tamoxifen (comparison 15)
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) used prolonged administration of mifepristone/prostaglandin. The dose regimens in the 2 groups were different and no meaningful conclusion could be made. Koopersmith (Koopersmith 1996) compared misoprostol alone to misoprostol/ tamoxifen and misoprostol/ laminaria. The sample size was very small and no meaningful conclusions could be made. For reasons of completeness these 2 trials were included in the tables.

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 regime was licensed for sale in Great Britain and France and rather sought to determine if a lower dose and less costly regimen can 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 be able to synthesise the included data the trials were grouped 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 fact of using 2 different pharmaceutical agents, in differing doses and different routes of application and most metaanalyses contain only a small number of reasonably comparable trials. We therefore focused on the primary outcome of effectiveness and were unable to draw firm conclusions on the associated side effects or relatively uncommon complications, such as continuing pregnancy or haemorrhage.

We can conclude 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 does not seem to be affected by lowering the dose from previously recommended 600 mg to 200 mg when combined with misoprostol of at least at 400 mcg. In earlier studies it has been shown that the linear dose-response effect of mifepristone does not occur in doses above 100 mg (Beaulieu 1996).

With regard to the role of gestational age, failure rates have been described to increase with gestational age, with at least a doubling in failure rate when comparing abortion at =/< 7 weeks to those at 9 weeks or more (WHO M400po). There was not sufficient data available from this review to confirm.

A **combination** regimen with a prostaglandin is more effective than prostaglandin alone. When split into subgroups of early and late first trimester, this effect was not apparent, but this may be due to the small numbers in each group. Similarly, mifepristone alone is less effective than a combination regimen with prostaglandin.

Different routes of application have been used, and **vaginal application of misoprostol** seems to be superior to oral administration being more effective and having less side effects.

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

Major complications seem to be rare, the most common one being blood transfusion (about 0.2%)(see table' characteristics of included studies'). The side effects are mainly due to prostaglandins (nausea, vomiting, diarrhoea). Different prostaglandins have been used, and the data included in the review does not allow one to conclude that any one is superior to another with regard to effectiveness. However, the dose and type of prostaglandin used may be important, as higher doses are associated with increased side effects such as nausea and vomiting.

The applicability of these results to under- resourced settings can be questioned. In most of the trials included, the inclusion criteria were strict, intrauterine pregnancy was confirmed by ultrasound, emergency back-up facilities were available and follow-up was high. These are all prerequisites that make the procedure safe and may not be available in poorer settings where the procedure could be associated with higher risk even if the drugs were available. The relatively high cost of mifepristone is another barrier to implementing this practice in under-resourced settings.

There are anecdotal data on the acceptability of different application routes and they may be linked to age, parity or cultural differences. The difference in delay of the administration of prostaglandin may play a role in the acceptability of one method over the other.

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

AUTHORS' CONCLUSIONS

Implications for practice

The available data from this review shows that the combination mifepristone/misoprostol is a safe and effective method to terminate pregnancy 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 metotrexate/prostaglandin regimen is scarce.

It is not clear if the regimen could be implemented where back-up facilities are not available and women are less likely to attend for the follow up. However, in settings where the resources are available, medical methods could be offered alongside surgical methods.

Implications for research

Methotrexate in combination with a prostaglandin may be an alternative to the mifepristone/prostaglandin regimen in places were 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 addressing side effects, bleeding patterns, acceptability or financial impact of the different methods.

Good quality acceptability studies are important to investigate the components that affect acceptability in different settings.

POTENTIAL CONFLICT OF INTEREST

None

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Baird 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 200 mg (all) and: group 1: gemeprost 0.5 mg vaginally and 3 tabs placebo after 48 hours group 2: misoprostol 600 mcg orally 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)
Allocation concealment	B – Unclear

Study	Bartley 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 200 mg (all) and group 1: gemeprost 500 mcg/pv group 2: misoprostol 800 mcg/pv
Outcomes	complete, incomplete abortion, ongoing pregnancy, duration of bleeding, side effects
Notes	single blinded 2 women required blood transfusions (1 in each group)
Allocation concealment	B – Unclear

Study	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 10 mg / twice daily for 7 days group 2: mifepristone 25 mg / twice daily for 7 days

Characteristics of included studies (*Continued*)

	group 3: mifepristone 50 mg / 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
Allocation concealment	B – Unclear

Study	**Cameron 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 150 mg / daily for 4 days group 2: mifepristone 150 mg and gemeprost 1-2 mg vaginally 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)
Allocation concealment	B – Unclear

Study	**Carbonell 97 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 50 mg/m2 intramuscular on recruitment day and misoprostol 800 mcg vaginally (self administered) on: group 1: day 3 group 2: day 4 group 3: day 5 additional 800 mcg 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
Allocation concealment	B – Unclear

Study	**Carbonell 98 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

Characteristics of included studies (*Continued*)

Interventions	methotrexate 50 mg orally on recruitment day and misoprostol 800 mcg vaginally (self administered) on: group 1: day 3 group 2: day 4 group 3: day 5 additional 800 mcg 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
Allocation concealment	A – Adequate

Study	**Cheng 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 100 mg/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
Allocation concealment	A – Adequate

Study	**Creinin 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 50 mg/m2 intramuscular and misoprostol 800 mcg/vaginally after 3 days group 2: misoprostol 800 mcg/vaginally
Outcomes	complete abortion, duration of vaginal bleeding, side effects, change in beta-HCG levels
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
Allocation concealment	A – Adequate

Study	**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 100 mg (all) after 2 days, home administration: group 1: misoprostol 400 mcg /po group 2: misoprostol 800 mcg /pv
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
Allocation concealment	A – Adequate

Study	**Creinin 95 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 50 mg/m2 intramuscular and: group 1: misoprostol 800 mcg/vaginally after 3 days group 2: misoprostol 800 mcg/vaginally 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
Allocation concealment	A – Adequate

Study	**Creinin 96 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 25 mg/orally followed by misoprostol 800 mcg/vaginally after 7 days group 2: methotrexate 50 mg/orally followed by misoprostol 800 mcg/vaginally after 7 days
Outcomes	complete abortion, duration of vaginal bleeding, side effects, change in haemoglobin/aspartate transferase
Notes	no major complications occurred
Allocation concealment	A – Adequate

Study	**Creinin 97 M800pv**
Methods	randomisation according to computer-generated random number table numbered sealed, opaque envelopes prepared by a person unrelated to the study no blinding

Characteristics of included studies (*Continued*)

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 50 mg/m2 followed by misoprostol 800 mcg/vaginally after 7 days group 2: methotrexate 60 mg/m2 followed by misoprostol 800 mcg/vaginally 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
Allocation concealment	A – Adequate

Study	**Creinin 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 600 mg (all) group 1: misoprostol 400 mcg after 6-8 hours/po group 2: misoprostol 400 mcg after 48 hours/po
Outcomes	complete abortion, onset and duration of bleeding, side effects
Notes	no blinding no major complications were reported
Allocation concealment	A – Adequate

Study	**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 200 mg and misoprostol 800 mcg/orally after 48 hours group 2: mifepristone 200 mg and misoprostol 400 mcg after 48 hours plus 400 mcg 2 hours later/orally
Outcomes	changes in blood pressure, pulse rate and temperature 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
Allocation concealment	A – Adequate

Study	**El-Refaey M800MI600**
Methods	computer generated random assignment before misoprostol administration, sealed opaque envelopes
Participants	270 women =/< 63 days of amenorrhoea, confirmed by ultrasound

Characteristics of included studies (*Continued*)

	Exclusion criteria: contraindication for the use of mifepristone and/or misoprostol
Interventions	group 1: mifepristone 600 mg and misoprostol 800 mcg/orally after 48 hours group 2: mifepristone 600 mg and misoprostol 800 mcg/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 blood transfusion (group 2)
Allocation concealment	A – Adequate

Study	**Jain 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 200 mg Group 2: Placebo both groups: misoprostol 800 mcg/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
Allocation concealment	A – Adequate

Study	**Jain 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 20 mg/twice daily and misoprostol 800 mcg/pv after 48 hours group 2: placebo twice daily and misoprostol 800 mcg/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
Allocation concealment	B – Unclear

Study	**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 100 mcg/vaginally/ 8 hourly to a maximum of 6 doses group B: misoprostol 100 mcg/vaginally/ 8 hourly to a maximum of 6 doses and tamoxifen 10 mg/orally after the first dose of misoprostol group C: misoprostol 100 mcg/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
Allocation concealment	B – Unclear

Study	**McKinley M600po**
Methods	identical envelopes, shuffled and numbered consecutively
Participants	220 pregnant women, =/< 63 days of amenorrhoea, University hospital Edinburgh, Scotland
Interventions	group 1: mifepristone 200 mg and misoprostol 600 mcg/orally after 48 hours group 2: mifepristone 600 mg and misoprostol 600 mcg/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
Allocation concealment	B – Unclear

Study	**Ozeren 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 < g/L, leucocytaemie, active liver disease, active renal disease, inflammatory bowel disease, history of methotrexate/ misoprostol intolerance
Interventions	group 1. methotrexate 50 mg/m2 / imi group 2: misoprostol 800 mcg/pv group 3: methotrexate 50 mg/m2/imi and misoprostol 800 mcg/pv after 3 days
Outcomes	complete abortions, ongoing pregnancies, side effects
Notes	no major complications were reported
Allocation concealment	A – Adequate

Study	**Rodger MI600**
Methods	randomisation not stated
Participants	120 pregnant women, <56 days of amenorrhoea, Gynaecological Out-Patient Department, Royal Infirmary Hospital, Edinburgh, Scotland
Interventions	mifepristone 600 mg (all) group 1: gemeprost 0.5 mg/pv after 48 hours group 2: gemeprost 1 mg/pv after 48 hours
Outcomes	complete, incomplete abortion, onset and duration of bleeding,

Characteristics of included studies (*Continued*)

	side effects, haemoglobin levels
Notes	1 woman received blood transfusion (group 2)
Allocation concealment	B – Unclear

Study	**Sandstrom 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 600 mg group1: gemeprost 1mg/pv after 24 hours group 2: gemeprost 1 mg/pv after 48 hours
Outcomes	complete, incomplete abortion, side effects
Notes	1 woman needed blood transfusion, not mentioned what group
Allocation concealment	B – Unclear

Study	**Sang 94 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 150 mg divided into 5 doses, orally, within 3 days; misoprostol 600 mcg orally 36-48 hours later group 2: mifepristone 150 mg divided into 5 doses /po, within 3 days; PGF2alpha /pv 36-48 hours later group 3: mifepristone 200 mg po; misoprostol 600 mcg/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
Allocation concealment	B – Unclear

Study	**Sang 99 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 150 mg divided into 5 doses taken orally within 3 days group 1: prostaglandin F2alpha 1 mg/pv 36-48 h after first dose of mifepristone group 2: misoprostol 600 mcg/po 36-48 h after first dose of mifepristone
Outcomes	complete, incomplete abortion, duration of vaginal bleeding, time to resume menses, side effects, women's satisfaction with the procedure
Notes	1 woman had allergic shock after misoprostol (group 2)
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Schaff 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 200 mg on day 1 group 1: 800 mcg misoprostol/po minimum 24 hours after at home group 2: misoprostol 400 mcg/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
Allocation concealment	B – Unclear

Study	**Schaff MI200M800**
Methods	computer generated random assignment, allocation, randomisation stratified by sites, allocation was 'concealed'
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 200 mg on day 1 group 1: misoprostol 800 mcg/pv next day at home group 2: misoprostol 800 mcg/pv 2 days later at home group 3: misoprostol 800 mcg/pv 3 days later at home
Outcomes	complete abortion, acceptability, adverse effects
Notes	2 women received blood transfusion (not mentioned which group)
Allocation concealment	B – Unclear

Study	**Swahn MI200MP1po**
Methods	randomly allocated
Participants	42 pregnant women, =/< 49 days of amenorrhoea, confirmed by ultrasound
Interventions	all: mifepristone 25 mg/twice daily/ for 4 days and: group 1: 1 placebo a.m. and p.m./orally 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
Allocation concealment	B – Unclear

Study	**Tang M800MI200**
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 800 mcg/po and misoprostol 400 mcg/X2/day/po for day 4-10 group B: misoprostol 800 mcg/pv on day 3 and misoprostol 400 mcg/X2/day/po for day 4 -10 group C: misoprostol 800 mcg/pv on day 3 and placebo tablets on day 4-10
Outcomes	complete, incomplete, missed abortion, ongoing pregnancy, blood loss, haemoglobin levels
Notes	no mentioning of major complications
Allocation concealment	B – Unclear

Study	**WHO 01 GP1pv**
Methods	computer generated sequence of random numbers in block of ten, 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
Allocation concealment	A – Adequate

Study	**WHO 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, breast-feeding, 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,

Characteristics of included studies (*Continued*)

	side effects
Notes	identical placebos, identical pill bottles; power calculation (90% power, significance level of 0.05) no major complications were reported
Allocation concealment	A – Adequate

Study	**WHO 00 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
Interventions	group 1: mifepristone 200 mg/oral group 2: mifepristone 400 mg/oral group 3: mifepristone 600 mg/oral and prostaglandin 1 mg/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
Allocation concealment	A – Adequate

Study	**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 25 mg/twice daily for 3 days and sulprostone 0.25 mg /intramuscular/ on third day a.m. group 2: mifepristone 25 mg /twice daily for 4 days and sulprostone 0.25 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)

Characteristics of included studies (*Continued*)

Notes	2 women received blood transfusion; not mentioned which group
Allocation concealment	B – Unclear

Study	**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 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 25 mg/12 hourly/ 5 doses and gemeprost 1 mg/vaginally 60 hours after the start of the treatment group 2: mifepristone 600 mg/single dose and gemeprost 1 mg/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
Allocation concealment	A – Adequate

Study	**WHO 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 50 mg/po and gemeprost 0.5 mg/pv on day 3 group 2: mifepristone 50 mg/po and gemeprost 1.0 mg/pv on day 3 group 3: mifepristone 200 mg/po and gemeprost 0.5 mg/pv on day 3 group 4: mifepristone 200 mg/po and gemeprost 1.0 mg/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)
Allocation concealment	A – Adequate

Study	**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.

Characteristics of included studies (*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
Allocation concealment	B – Unclear

Study	**Wiebe 1999**
Methods	computer generated list of random numbers, sealed, opaque envelopes
Participants	398 women, =/< 7 weeks pregnant confirmed by ultrasound, University Hospital Vancouver, Canada exclusion criteria: abnormal haematologic parameters
Interventions	Phase 1: group 1: Tamoxifen 40 mg/po and 800 mcg misoprostol/pv > 48 hours group 2: Methotrexate 50 mg/m2 and misoprostol 800 mcg/pv >96 hours Phase 2: group 1: Tamoxifen 40 mg/day for 4 days (= total dose of 160 mg) and misoprostol 800 mcg/pv > 48 hours group 2: Methotrexate 50 mg/m2 and misoprostol 800 mcg/pv >96 hours
Outcomes	failure rate, side effects, women's preference
Notes	no major complications were reported
Allocation concealment	A – Adequate

Study	**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 160 mg) and misoprostol 800 mcg/pv > 48 hours group 2: Methotrexate 50 mg/m2 and misoprostol 800 mcg/pv >96 hours
Outcomes	see Wiebe 1999
Notes	see Wiebe 1999
Allocation concealment	A – Adequate

Study	**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
Interventions	group 1: methotrexate 50 mg/m2/po and misoprostol 600 mcg/pv > 96 hours

	group 2: methotrexate 50 mg/m2/imi and misoprostol 600 mcg/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
Allocation concealment	A – Adequate

Study	**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 200 mg and tamoxifen 40 mg/po day 2: tamoxifen 40 mg/po day 3: PGF2alpha /pv group 2: day 1: mifepristone 200 mg and placebo/po day 2: placebo /po 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
Allocation concealment	B – Unclear

Study	**Zheng 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 600 mg group 2: mifepristone 600 mg 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
Allocation concealment	B – Unclear

Characteristics of excluded studies

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

Characteristics of excluded studies (*Continued*)

Davis 1999	Data for one group (Methotrexate) was reported for all (randomised and non-randomised) women together
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

ANALYSES

Comparison 01. combined regimen mifepristone/prostaglandin: dose of mifepristone: 600mg vs 200mg

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion	4	3482	Relative Risk (Fixed) 95% CI	1.07 [0.87, 1.32]
02 side effects			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 02. combined regimen mifepristone/prostaglandin: dose of prostaglandin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 03. combined regimen mifepristone/prostaglandin: type of prostaglandin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 04. combined regimen mifepristone/prostaglandin: time of prostaglandin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion			Relative Risk (Fixed) 95% CI	Totals not selected
02 side effects			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 05. combined regimen mifepristone/prostaglandin: misoprostol po vs pv

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion	2	1407	Relative Risk (Fixed) 95% CI	4.41 [2.32, 8.38]
02 side effects			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 06. combined regimen mifepristone/prostaglandin: single vs split dose prostaglandin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion	1	154	Relative Risk (Fixed) 95% CI	0.70 [0.21, 2.39]
02 side effects			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 07. mifepristone alone vs combined regimen mifepristone/prostaglandin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion	3	273	Relative Risk (Fixed) 95% CI	3.76 [2.30, 6.15]

Comparison 08. prostaglandin alone vs combined regimen (all)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion			Relative Risk (Fixed) 95% CI	Totals not selected
02 side effects			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 09. mifepristone single - high vs low dose

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion	1	101	Relative Risk (Fixed) 95% CI	1.32 [0.74, 2.38]
02 side effects			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 10. combined regimen methotrexate/prostaglandin: timing of prostaglandin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 11. combined regimen methotrexate/prostaglandin: methotrexate imi vs po

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion	1	100	Relative Risk (Fixed) 95% CI	2.04 [0.51, 8.07]
02 Side effects			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 12. combined regimen methotrexate/prostaglandin: dose of methotrexate

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion			Relative Risk (Fixed) 95% CI	Totals not selected
02 side effects	0	0	Odds Ratio (Fixed) 95% CI	Not estimable

Comparison 13. tamoxifen vs methotrexate (combined with prostaglandin) : low dose tamoxifen (40 mg)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion	1	198	Relative Risk (Fixed) 95% CI	2.04 [0.86, 4.84]
02 side effects			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 14. tamoxifen vs methotrexate (combined with prostaglandin): high dose tamoxifen (160 mg)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion	1	200	Relative Risk (Fixed) 95% CI	1.96 [0.93, 4.15]
02 side effects			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 15. combined regimen mifepristone/prostaglandin vs mifepristone/prostaglandin and tamoxifen

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 failure to achieve complete abortion			Relative Risk (Fixed) 95% CI	Totals not selected

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; Tamoxifen [administration & dosage]

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title Medical methods for first trimester abortion

Authors	Kulier R, Gülmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A
Contribution of author(s)	RK had the idea and wrote the review. AMG, GJH, CLN and AC reviewed and contributed substantially in all aspects of the review.
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What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 combined regimen mifepristone/prostaglandin: dose of mifepristone: 600mg vs 200mg, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 01 combined regimen mifepristone/prostaglandin: dose of mifepristone: 600mg vs 200mg

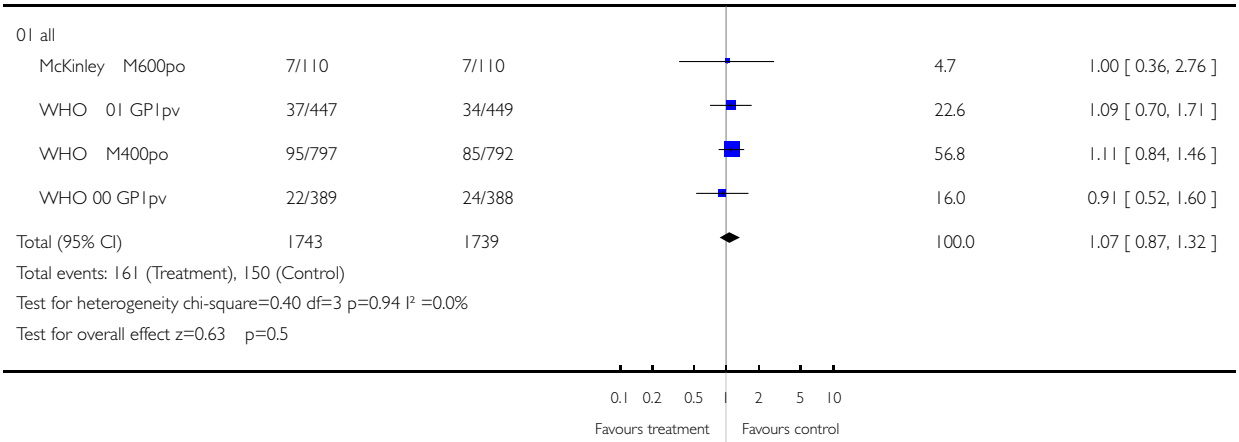
Outcome: 01 failure to achieve complete abortion

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 all					
McKinley M600po	7/110	7/110		4.7	1.00 [0.36, 2.76]
WHO 01 GP1pv	37/447	34/449		22.6	1.09 [0.70, 1.71]
WHO M400po	95/797	85/792		56.8	1.11 [0.84, 1.46]
WHO 00 GP1pv	22/389	24/388		16.0	0.91 [0.52, 1.60]
Total (95% CI)	1743	1739		100.0	1.07 [0.87, 1.32]

Total events: 161 (Treatment), 150 (Control)

Test for heterogeneity chi-square=0.40 df=3 p=0.94 I^2 =0.0%

Test for overall effect z=0.63 p=0.5



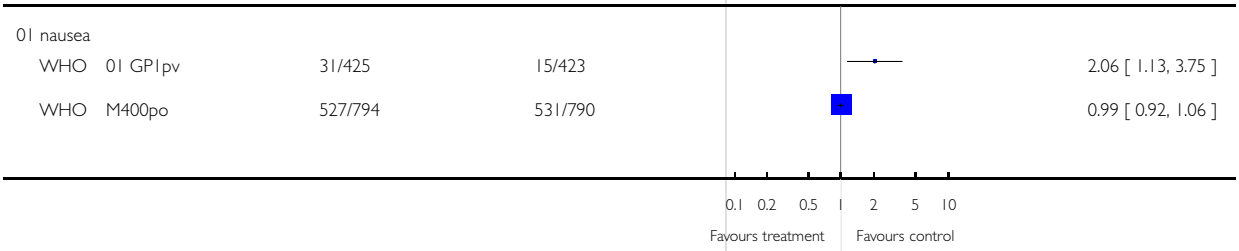
Analysis 01.02. Comparison 01 combined regimen mifepristone/prostaglandin: dose of mifepristone: 600mg vs 200mg, Outcome 02 side effects

Review: Medical methods for first trimester abortion

Comparison: 01 combined regimen mifepristone/prostaglandin: dose of mifepristone: 600mg vs 200mg

Outcome: 02 side effects

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
01 nausea				
WHO 01 GP1pv	31/425	15/423		2.06 [1.13, 3.75]
WHO M400po	527/794	531/790		0.99 [0.92, 1.06]



Analysis 02.01. Comparison 02 combined regimen mifepristone/prostaglandin: dose of prostaglandin, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 02 combined regimen mifepristone/prostaglandin: dose of prostaglandin

Outcome: 01 failure to achieve complete abortion

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 gemeprost 1 mg vs 0.5 mg					
Rodger MI600	0/30	1/30		2.1	0.33 [0.01, 7.87]
WHO MI200/50	57/650	66/574		97.9	0.76 [0.54, 1.07]
Subtotal (95% CI)	680	604		100.0	0.75 [0.54, 1.05]
Total events: 57 (Treatment), 67 (Control)					
Test for heterogeneity chi-square=0.26 df=1 p=0.61 I^2 =0.0%					
Test for overall effect z=1.66 p=0.1					

Analysis 03.01. Comparison 03 combined regimen mifepristone/prostaglandin: type of prostaglandin, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 03 combined regimen mifepristone/prostaglandin: type of prostaglandin

Outcome: 01 failure to achieve complete abortion

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
01 gemeprost vs misoprostol				
Baird GP0.5 M600po	13/391	21/386		0.61 [0.31, 1.20]
Bartley GP0.5M800pv	17/453	6/457		2.86 [1.14, 7.18]
02 PGF2alpha vs misoprostol				
Sang 94 M600poPGF2pv	4/150	17/301		0.47 [0.16, 1.38]
Sang 99 M600poPGF2pv	674/9934	512/7589		1.01 [0.90, 1.12]

Analysis 04.01. Comparison 04 combined regimen mifepristone/prostaglandin: time of prostaglandin, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 04 combined regimen mifepristone/prostaglandin: time of prostaglandin

Outcome: 01 failure to achieve complete abortion

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
01 day 3 vs day 1				
Schaff MI200M800	30/755	15/734		1.94 [1.05, 3.58]
02 day 3 vs day 2				
Schaff MI200M800	30/755	18/766		1.69 [0.95, 3.01]
03 day 2 vs day 1				
Sandstrom MI600GP1pv	5/33	4/31		1.17 [0.35, 3.98]
Schaff MI200M800	18/766	15/734		1.15 [0.58, 2.26]
04 day 2 vs day 0				
Creinin MI600 M400	1/44	2/42		0.48 [0.04, 5.07]

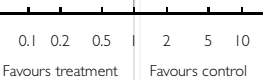
Analysis 04.02. Comparison 04 combined regimen mifepristone/prostaglandin: time of prostaglandin, Outcome 02 side effects

Review: Medical methods for first trimester abortion

Comparison: 04 combined regimen mifepristone/prostaglandin: time of prostaglandin

Outcome: 02 side effects

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
01 nausea day 3 vs day 1				
Schaff MI200M800	414/654	426/704		1.05 [0.96, 1.14]
02 nausea day 3 vs day 2				
Schaff MI200M800	414/654	471/730		0.98 [0.91, 1.06]
03 nausea day 2 vs day 1				
Schaff MI200M800	471/730	426/704		1.07 [0.98, 1.16]
04 nausea day 2 vs day 0				
Creinin MI600 M400	18/43	23/42		0.76 [0.49, 1.20]
05 vomiting day 3 vs day 1				
Schaff MI200M800	205/654	218/704		1.01 [0.86, 1.19]
06 vomiting day 3 vs day 2				



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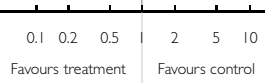
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
Schaff MI200M800	205/654	237/730		0.97 [0.83, 1.13]
07 vomiting day 2 vs day 1				
Schaff MI200M800	237/730	218/704		1.05 [0.90, 1.22]
08 vomiting day 2 vs day 0				
Creinin MI600 M400	6/43	5/42		1.17 [0.39, 3.55]
09 diarrhoea day 3 vs day 1				
Schaff MI200M800	155/654	138/704		1.21 [0.99, 1.48]
10 diarrhoea day 3 vs day 2				
Schaff MI200M800	155/654	149/730		1.16 [0.95, 1.42]
11 diarrhoea day 2 vs day 1				
Schaff MI200M800	149/730	138/704		1.04 [0.85, 1.28]
12 diarrhoea day 2 vs day 0				
Creinin MI600 M400	8/43	15/42		0.52 [0.25, 1.10]



Analysis 05.01. Comparison 05 combined regimen mifepristone/prostaglandin: misoprostol po vs pv, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 05 combined regimen mifepristone/prostaglandin: misoprostol po vs pv

Outcome: 01 failure to achieve complete abortion

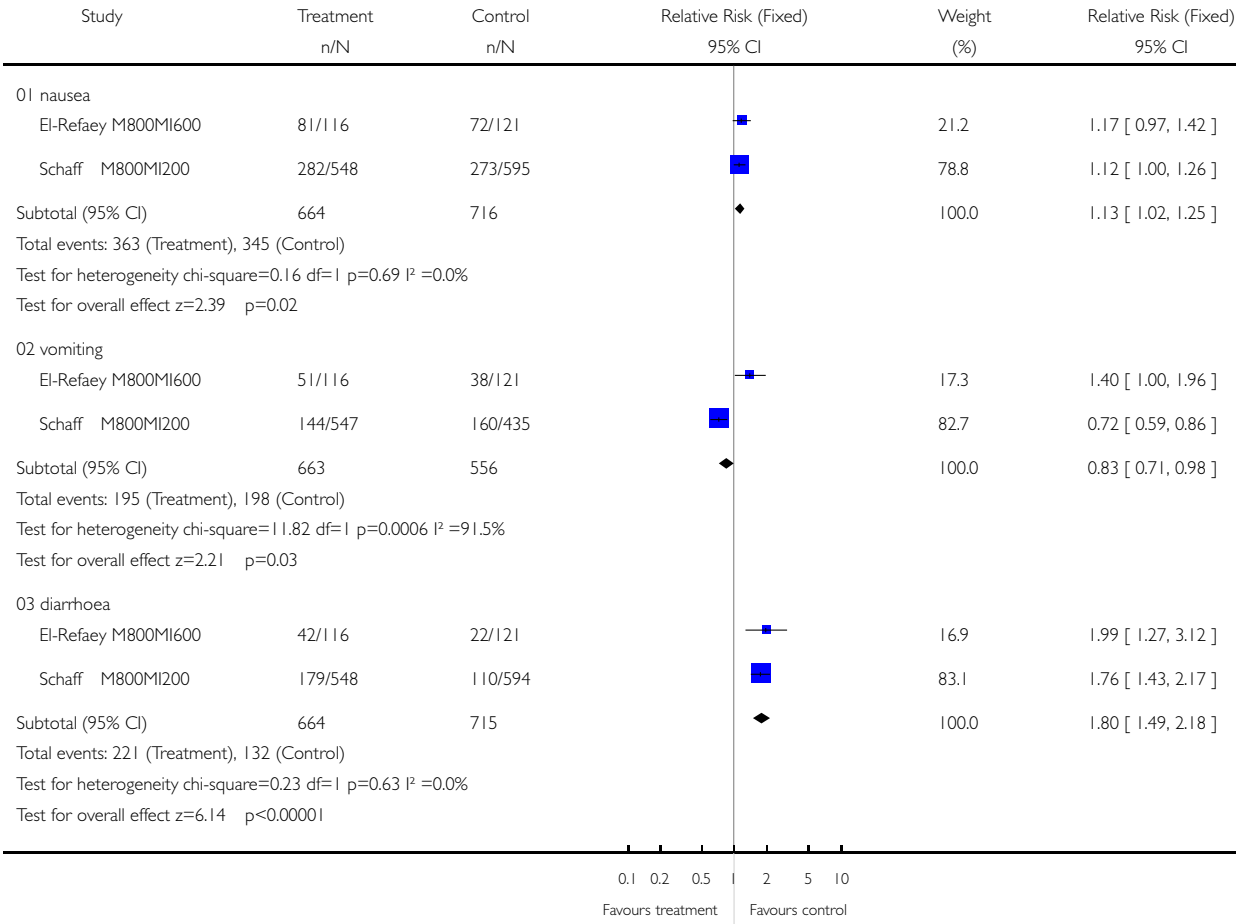
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
El-Refaey M800MI600	17/130	7/133		64.4	2.48 [1.07, 5.79]
Schaff M800MI200	29/548	4/596		35.6	7.89 [2.79, 22.28]
Total (95% CI)	678	729		100.0	4.41 [2.32, 8.38]
Total events: 46 (Treatment), 11 (Control)					
Test for heterogeneity chi-square=2.97 df=1 p=0.08 I^2 =66.3%					
Test for overall effect z=4.53 p<0.00001					

Analysis 05.02. Comparison 05 combined regimen mifepristone/prostaglandin: misoprostol po vs pv, Outcome 02 side effects

Review: Medical methods for first trimester abortion

Comparison: 05 combined regimen mifepristone/prostaglandin: misoprostol po vs pv

Outcome: 02 side effects



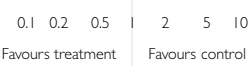
Analysis 06.01. Comparison 06 combined regimen mifepristone/prostaglandin: single vs split dose prostaglandin, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 06 combined regimen mifepristone/prostaglandin: single vs split dose prostaglandin

Outcome: 01 failure to achieve complete abortion

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
El-Refaey 1994	4/75	6/79		100.0	0.70 [0.21, 2.39]
Total (95% CI)	75	79		100.0	0.70 [0.21, 2.39]
Total events: 4 (Treatment), 6 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.57 p=0.6					



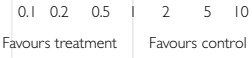
Analysis 06.02. Comparison 06 combined regimen mifepristone/prostaglandin: single vs split dose prostaglandin, Outcome 02 side effects

Review: Medical methods for first trimester abortion

Comparison: 06 combined regimen mifepristone/prostaglandin: single vs split dose prostaglandin

Outcome: 02 side effects

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
01 nausea				
El-Refaey 1994	51/75	44/75		1.16 [0.91, 1.48]
02 vomiting				
El-Refaey 1994	30/75	23/75		1.30 [0.84, 2.02]
03 diarrhoea				
El-Refaey 1994	25/75	16/75		1.56 [0.91, 2.68]



Analysis 07.01. Comparison 07 mifepristone alone vs combined regimen mifepristone/prostaglandin, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 07 mifepristone alone vs combined regimen mifepristone/prostaglandin

Outcome: 01 failure to achieve complete abortion

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cameron MI600GP1pv	8/20	1/19		6.3	7.60 [1.05, 55.14]
Swahn MI200MP1po	6/14	11/28		45.1	1.09 [0.51, 2.33]
Zheng MI600PGF2pv	45/95	8/97		48.6	5.74 [2.86, 11.53]
Total (95% CI)	129	144		100.0	3.76 [2.30, 6.15]
Total events: 59 (Treatment), 20 (Control)					
Test for heterogeneity chi-square=12.09 df=2 p=0.002 I^2 =83.5%					
Test for overall effect z=5.29 p<0.00001					

Analysis 08.01. Comparison 08 prostaglandin alone vs combined regimen (all), Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 08 prostaglandin alone vs combined regimen (all)

Outcome: 01 failure to achieve complete abortion

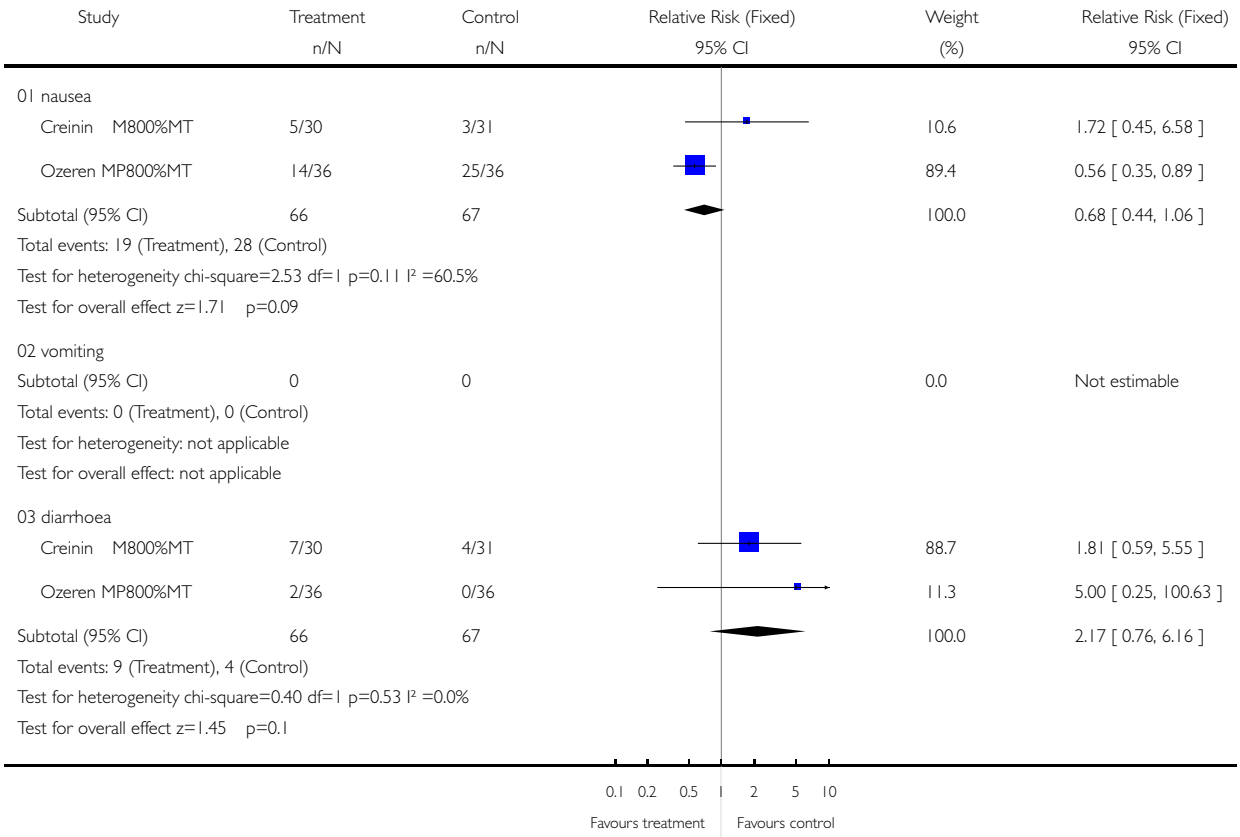
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
01 all				
Cheng PGE1%T	36/76	20/75		1.78 [1.14, 2.77]
Creinin M800%MT	16/30	3/31		5.51 [1.79, 17.00]
Jain M800%MI	15/125	5/119		2.86 [1.07, 7.61]
Jain M800%TM	7/75	5/75		1.40 [0.47, 4.21]
Ozeren MP800%MT	15/36	4/36		3.75 [1.38, 10.21]
02 =/< 49 days gestation				
Jain M800%MI	9/80	3/75		2.81 [0.79, 10.00]
03 > 49 days gestation				
Jain M800%MI	6/45	2/44		2.93 [0.63, 13.76]

Analysis 08.02. Comparison 08 prostaglandin alone vs combined regimen (all), Outcome 02 side effects

Review: Medical methods for first trimester abortion

Comparison: 08 prostaglandin alone vs combined regimen (all)

Outcome: 02 side effects

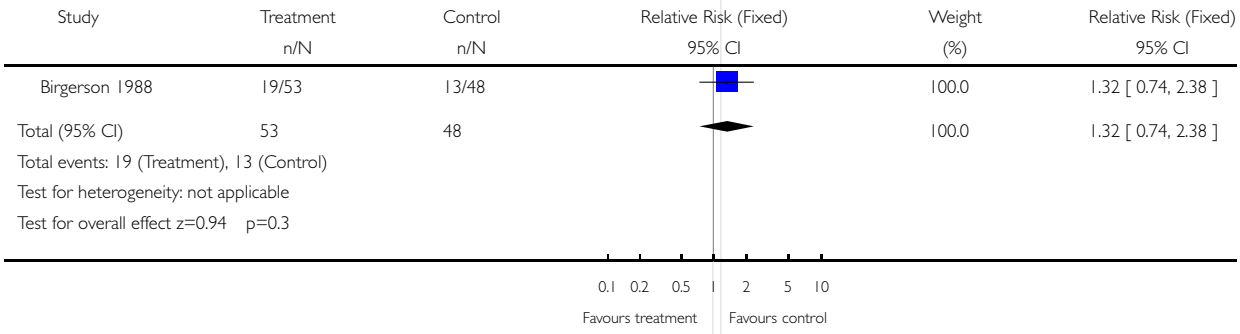


Analysis 09.01. Comparison 09 mifepristone single - high vs low dose, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 09 mifepristone single - high vs low dose

Outcome: 01 failure to achieve complete abortion



Analysis 09.02. Comparison 09 mifepristone single - high vs low dose, Outcome 02 side effects

Review: Medical methods for first trimester abortion

Comparison: 09 mifepristone single - high vs low dose

Outcome: 02 side effects

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 nausea					
Birgerson 1988	8/53	18/48		100.0	0.40 [0.19, 0.84]
Subtotal (95% CI)	53	48		100.0	0.40 [0.19, 0.84]
Total events: 8 (Treatment), 18 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.42 p=0.02					
02 vomiting					
Birgerson 1988	2/53	5/48		100.0	0.36 [0.07, 1.78]
Subtotal (95% CI)	53	48		100.0	0.36 [0.07, 1.78]
Total events: 2 (Treatment), 5 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.25 p=0.2					

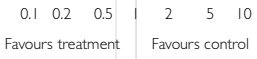
Analysis 10.01. Comparison 10 combined regimen methotrexate/prostaglandin: timing of prostaglandin, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 10 combined regimen methotrexate/prostaglandin: timing of prostaglandin

Outcome: 01 failure to achieve complete abortion

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 misoprostol day 7 vs day 3					
Creinin 95 M800pv	1/40	8/46		100.0	0.14 [0.02, 1.10]
Subtotal (95% CI)	40	46		100.0	0.14 [0.02, 1.10]
Total events: 1 (Treatment), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.87 p=0.06					
02 misoprostol day 5 vs day 3					
Carbonell 97 M800pv	7/96	7/93		39.5	0.97 [0.35, 2.65]
Carbonell 98 M800pv	6/98	11/100		60.5	0.56 [0.21, 1.45]
Subtotal (95% CI)	194	193		100.0	0.72 [0.36, 1.43]



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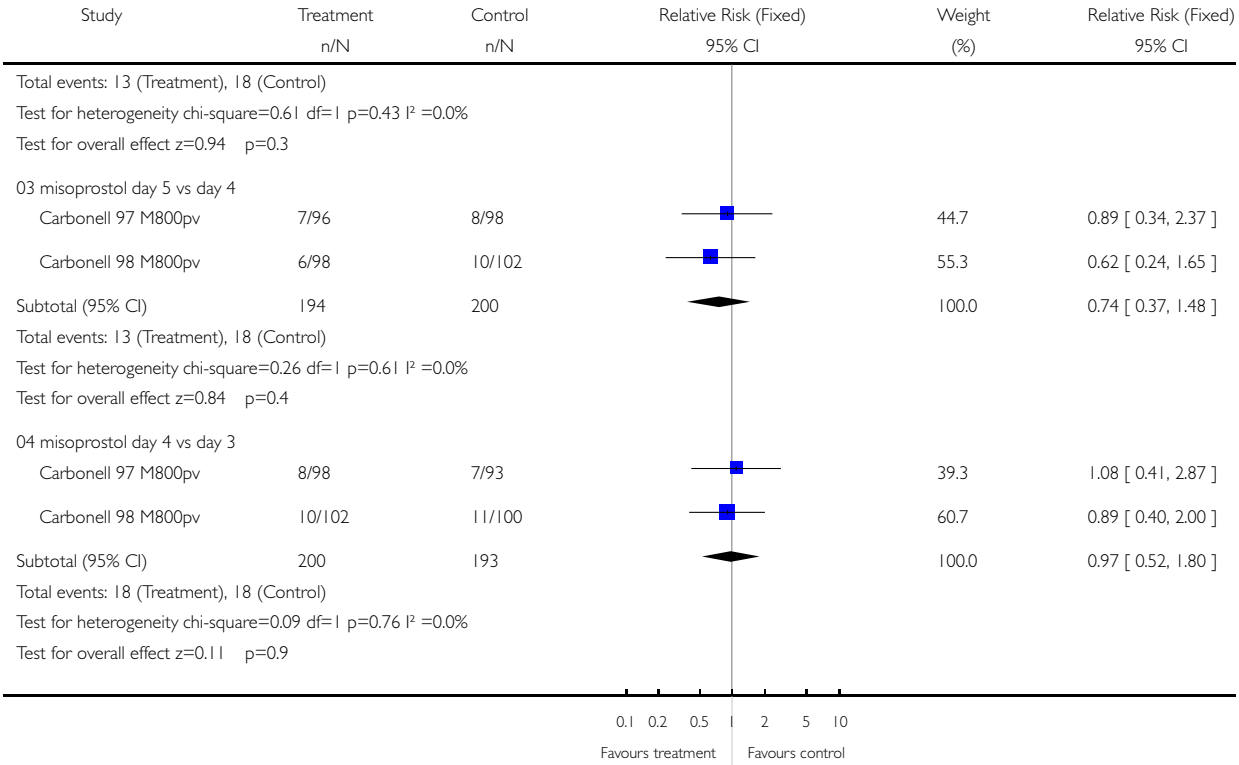
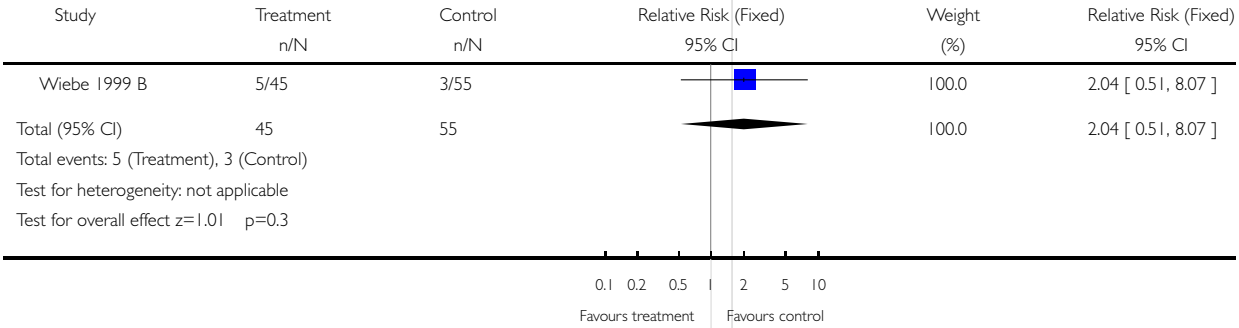


Analysis 11.01. Comparison 11 combined regimen methotrexate/prostaglandin: methotrexate imi vs po, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 11 combined regimen methotrexate/prostaglandin: methotrexate imi vs po

Outcome: 01 failure to achieve complete abortion

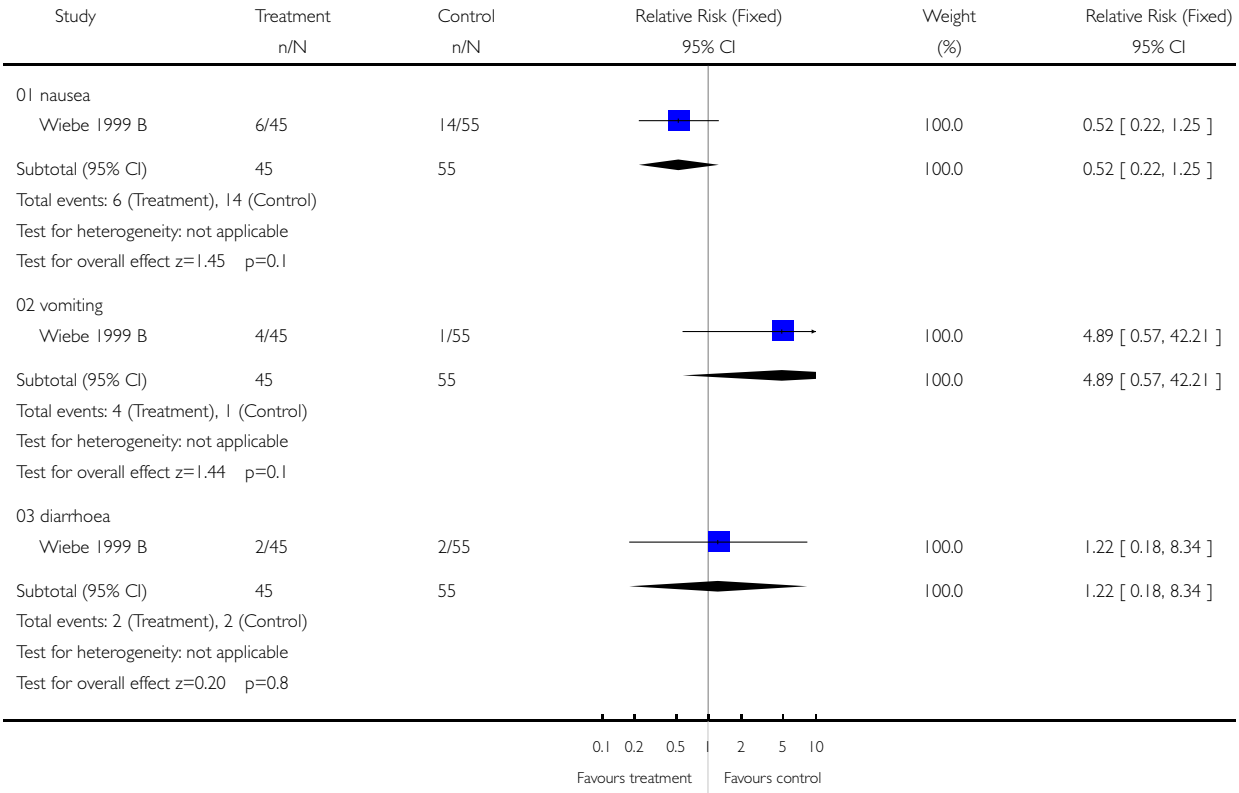


Analysis 11.02. Comparison 11 combined regimen methotrexate/prostaglandin: methotrexate imi vs po, Outcome 02 Side effects

Review: Medical methods for first trimester abortion

Comparison: 11 combined regimen methotrexate/prostaglandin: methotrexate imi vs po

Outcome: 02 Side effects

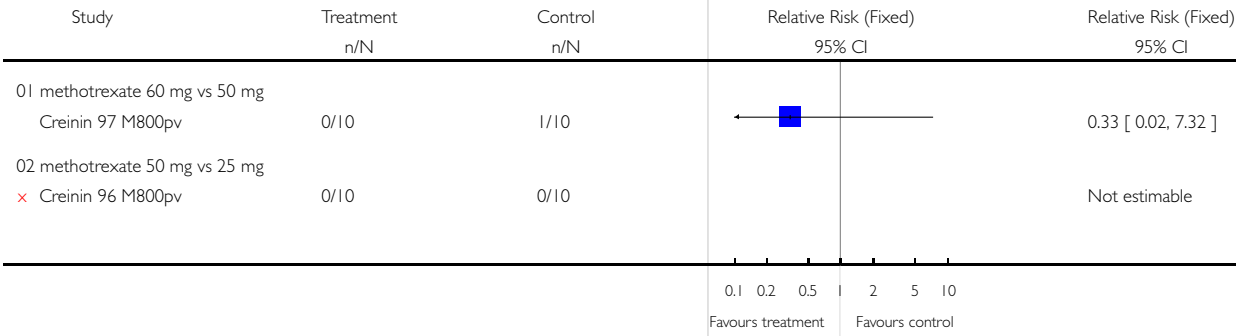


Analysis 12.01. Comparison 12 combined regimen methotrexate/prostaglandin: dose of methotrexate, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 12 combined regimen methotrexate/prostaglandin: dose of methotrexate

Outcome: 01 failure to achieve complete abortion



Analysis 13.01. Comparison 13 tamoxifen vs methotrexate (combined with prostaglandin) : low dose tamoxifen (40 mg), Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 13 tamoxifen vs methotrexate (combined with prostaglandin) : low dose tamoxifen (40 mg)

Outcome: 01 failure to achieve complete abortion

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Wiebe 1999	14/98	7/100		100.0	2.04 [0.86, 4.84]
Total (95% CI)	98	100		100.0	2.04 [0.86, 4.84]
Total events: 14 (Treatment), 7 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.62 p=0.1					

Analysis 13.02. Comparison 13 tamoxifen vs methotrexate (combined with prostaglandin) : low dose tamoxifen (40 mg), Outcome 02 side effects

Review: Medical methods for first trimester abortion

Comparison: 13 tamoxifen vs methotrexate (combined with prostaglandin) : low dose tamoxifen (40 mg)

Outcome: 02 side effects

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 nausea					
Wiebe 1999	16/98	29/100		100.0	0.56 [0.33, 0.97]
Subtotal (95% CI)	98	100		100.0	0.56 [0.33, 0.97]
Total events: 16 (Treatment), 29 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.07 p=0.04					
02 vomiting					
Wiebe 1999	5/98	3/100		100.0	1.70 [0.42, 6.92]
Subtotal (95% CI)	98	100		100.0	1.70 [0.42, 6.92]
Total events: 5 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.74 p=0.5					
03 diarrhoea					
Wiebe 1999	3/98	2/100		100.0	1.53 [0.26, 8.96]
Subtotal (95% CI)	98	100		100.0	1.53 [0.26, 8.96]
Total events: 3 (Treatment), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.47 p=0.6					

Analysis 14.01. Comparison 14 tamoxifen vs methotrexate (combined with prostaglandin): high dose tamoxifen (160 mg), Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 14 tamoxifen vs methotrexate (combined with prostaglandin): high dose tamoxifen (160 mg)

Outcome: 01 failure to achieve complete abortion

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Wiebe 1999 A	18/101	9/99		100.0	1.96 [0.93, 4.15]
Total (95% CI)	101	99		100.0	1.96 [0.93, 4.15]
Total events: 18 (Treatment), 9 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.76 p=0.08					

Analysis 14.02. Comparison 14 tamoxifen vs methotrexate (combined with prostaglandin): high dose tamoxifen (160 mg), Outcome 02 side effects

Review: Medical methods for first trimester abortion

Comparison: 14 tamoxifen vs methotrexate (combined with prostaglandin): high dose tamoxifen (160 mg)

Outcome: 02 side effects

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 nausea					
Wiebe 1999 A	34/101	43/99		100.0	0.78 [0.54, 1.10]
Subtotal (95% CI)	101	99		100.0	0.78 [0.54, 1.10]
Total events: 34 (Treatment), 43 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.41 p=0.2					
02 vomiting					
Wiebe 1999 A	8/101	12/99		100.0	0.65 [0.28, 1.53]
Subtotal (95% CI)	101	99		100.0	0.65 [0.28, 1.53]
Total events: 8 (Treatment), 12 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.98 p=0.3					
03 diarrhoea					
Wiebe 1999 A	5/101	4/99		100.0	1.23 [0.34, 4.43]
Subtotal (95% CI)	101	99		100.0	1.23 [0.34, 4.43]
Total events: 5 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.31 p=0.8					

Analysis 15.01. Comparison 15 combined regimen mifepristone/prostaglandin vs mifepristone/prostaglandin and tamoxifen, Outcome 01 failure to achieve complete abortion

Review: Medical methods for first trimester abortion

Comparison: 15 combined regimen mifepristone/prostaglandin vs mifepristone/prostaglandin and tamoxifen

Outcome: 01 failure to achieve complete abortion