

Simultaneous compared to interval administration of mifepristone and misoprostol for medical abortion up to 10⁺⁰ weeks' gestation: a systematic review with meta-analyses

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ABSTRACT

Background Medical abortion with mifepristone and misoprostol usually involves an interval of 36–48 hours between administering these drugs; however, it is possible that the clinical efficacy at early gestations may be maintained when the drugs are taken simultaneously. The objective of this systematic review was to determine the safety and effectiveness of simultaneous compared with interval administration of mifepristone and misoprostol for abortion up to 10⁺⁰ weeks' gestation.

Methods We searched Embase Classic, Embase; Ovid MEDLINE(R) including Daily, and Epub Ahead-of-Print, In-Process & Other Non-Indexed Citations; and Cochrane Library on 11 December 2019. We included randomised controlled trials (RCTs), published in English from 1985, comparing simultaneous to interval administration of mifepristone and misoprostol for early abortion. Risk of bias was assessed using the Cochrane Collaboration checklist for RCTs. Meta-analysis of risk ratios (RRs) using the Mantel-Haenszel method were performed. The quality of the evidence was assessed using GRADE.

Results Meta-analyses of three RCTs (n=1280) showed no differences in 'ongoing pregnancy' (RR 1.78, 95% CI 0.38 to 8.36), 'haemorrhage requiring transfusion or ≥500 mL blood loss' (RR 0.11, 95% CI 0.01 to 2.03) and 'incomplete abortion with the need for surgical intervention' (RR 1.30, 95% CI 0.76 to 2.25) between the interventions. Individual study results showed no difference in patient satisfaction, or 'need for repeat misoprostol', although 'time to onset of bleeding or cramping' was longer after

Key messages

- Early medical abortion usually involves a 36–48-hour interval between mifepristone and misoprostol administration; however, clinical efficacy may be maintained when the drugs are taken simultaneously.
- This systematic review examined the safety and effectiveness of simultaneous compared to interval administration of mifepristone and misoprostol for abortion up to 10⁺⁰ weeks' gestation.
- The published data (three randomised controlled trials; n=1280) support using simultaneous mifepristone and misoprostol for medical abortion up to 9⁺⁰ weeks in women who prefer this method of administration.

simultaneous than interval administration. The quality of evidence was very low to moderate.

Conclusion The published data support the use of simultaneous mifepristone and misoprostol for medical abortion up to 9⁺⁰ weeks in women who prefer this method of administration.

INTRODUCTION

Medical abortion using a combination of the progesterone receptor modulator mifepristone followed by the prostaglandin analogue misoprostol is a highly effective and safe method for abortion of pregnancy up to and including 10⁺⁰ weeks' gestation. Mifepristone sensitises

the uterus to the effects of prostaglandins and results in lower total doses of prostaglandins needed to induce abortion, and fewer related side effects. Studies have shown that an interval of 36–48 hours between the intake of mifepristone and administration of misoprostol results in optimal sensitisation of the uterus to exogenous prostaglandins with maximal effects on uterine contractility.¹ However, it is possible that although the synergistic effect of mifepristone and misoprostol may be best with an interval between the drugs, the clinical efficacy of abortion at early gestations may be maintained or only slightly reduced when the drugs are taken simultaneously.^{2–4}

The interval between administering the two drugs may be a disadvantage for women who need to complete the abortion procedure as quickly as possible, for example, due to difficulty in getting time off work or arranging child care, and for women who are forced to travel to other countries or settings for abortion because abortion is illegal or highly restricted where they live. In addition, in some settings women have to receive both drugs at a hospital or at a clinic that has a special license for abortion.⁵ This can result in an additional clinic visit and this was the situation throughout Great Britain until recently (2019).^{6–8} If simultaneous intake of mifepristone and misoprostol is shown to be a safe and effective alternative to interval treatment then this would increase the flexibility of the regimen and expand access to medical abortion for women.

OBJECTIVE

This systematic review was undertaken as part of the 2019 NICE guideline on abortion care.⁹ The aim of this study was to determine whether it is safe and effective to administer mifepristone and misoprostol simultaneously (defined as within 15 min) for abortion up to and including 10⁺ weeks' gestation compared with any interval administration of misoprostol after mifepristone.

METHODS

Eligibility criteria for considering studies in this review

Eligible studies were randomised controlled trials (RCTs), published in English from 1985 onwards. 1985 was selected as mifepristone was not licensed for use before this time. Eligible studies compared simultaneous (within 15 min) administration of mifepristone and misoprostol to any interval administration of misoprostol after mifepristone for abortion up to 10⁺ weeks' gestation, reporting any of the following outcomes: 'ongoing pregnancy', 'haemorrhage requiring transfusion or ≥500 mL blood loss', 'patient satisfaction', 'need for repeat misoprostol', 'time to onset of bleeding or cramping', 'total treatment time from mifepristone to expulsion', and 'incomplete abortion with the need for surgical intervention'. These outcomes were selected as the main outcomes

in the absence of any published core outcome set for abortion.

Information sources and search strategy

On 11 December 2019 we searched Embase Classic and Embase from 1947 to 10 December 2019; Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) from 1946 to 10 December 2019; and the Cochrane Library (Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)) via Wiley Online, using the search strategies detailed in online supplementary appendix S1, with a date limit of 1985 onwards. We also consulted experts in this field and checked review articles for any ongoing or missed trials.

Study selection and data extraction

One author screened the results of the computerised search, classifying the records into 'potentially relevant' and 'definitely not relevant' based on the titles and abstracts. The full-texts of the potentially relevant studies were examined by one author and classified into 'include' and 'exclude'. The final list of included studies was confirmed by consensus between three of the authors, and one of the authors extracted the following data from each of the included studies: country, dates, aim, inclusion and exclusion criteria, baseline characteristics, medical abortion details, and outcome data for each of the intervention groups.

Assessment of risk of bias

One author assessed the risk of bias in each of the studies. We used the Cochrane Collaboration quality checklist for randomised controlled trials¹⁰ with selection bias and outcome reporting bias assessed at study-level and performance bias, detection bias and attrition bias assessed at outcome-level.

Data synthesis

All the meta-analyses we were able to undertake were of risk ratios (RRs) and these dichotomous data were meta-analysed in Review Manager 5.3¹¹ using the Mantel-Haenszel statistical method and a fixed effect model as the I^2 was below 50% in all three analyses. We would have used a random effects model if the I^2 had been 50%–80%, and not pooled the risk ratios (but rather reported them individually for each study) had the I^2 been above 80%. This, however, did not occur. We had aimed to undertake subgroup analyses based on complex pre-existing medical conditions (none vs present), gestation ($\leq 6^{+0}$ vs 6^{+1} – 8^{+0} vs 8^{+1} – 10^{+0}) and location of pregnancy expulsion (home vs healthcare setting vs not defined), but the included studies did not report such data and therefore we were unable to perform these analyses.

Table 1 GRADE summary of findings table for the critical outcomes

Quality assessment			Patients (n)			Effect					
Studies (n)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous	Delayed	Relative risk (RR (95% CI))	Absolute	Quality
Ongoing pregnancy											
3	RCTs	Serious*	No serious inconsistency	No serious indirectness	Very serious†	None	4/694 (0.58%)	2/686 (0.29%)	1.78 (0.38 to 8.36)	2 more per 1000 (from 2 fewer to 21 more)	Very low
Haemorrhage requiring transfusion or 500 mL blood loss or above											
3	RCTs	Serious*‡	No serious inconsistency	No serious indirectness	Very serious§	None	0/694 (0%)	4/686 (0.58%)	0.11 (0.01 to 2.03)	5 fewer per 1000 (from 6 fewer to 6 more)	Very low
Patient satisfaction ("Would choose same method again")											
1	RCTs	Serious¶	No serious inconsistency	No serious indirectness	No serious imprecision	None	480/545 (88.1%)	477/536 (89%)	0.99 (0.95 to 1.03)	9 fewer per 1000 (from 44 fewer to 27 more)	Moderate
Patient satisfaction ("Would recommend to friend")											
1	RCTs	Serious¶	No serious inconsistency	No serious indirectness	No serious imprecision	None	512/545 (93.9%)	504/536 (94%)	1.00 (0.97 to 1.03)	0 fewer per 1000 (from 28 fewer to 28 more)	Moderate
Patient satisfaction ("Satisfied with procedure and would like to use this method again")											
1	RCTs	Serious¶**	No serious inconsistency	No serious indirectness	No serious imprecision	None	39/40 (97.5%)	38/40 (95%)	1.03 (0.94 to 1.12)	28 more per 1000 (from 57 fewer to 114 more)	Moderate

*Unclear randomisation sequence generation and/or allocation concealment adequacy in two of the three studies.

†The CI crosses 0.8 and 1.25.

‡All three studies were unblinded.

§The event rate <150.

¶Unblinded study.

**Unclear adequacy of allocation concealment.

RCT, randomised controlled trial.

Table 2 GRADE summary of findings table for the important outcomes

Quality assessment				Patients (n)		Effect						
Studies (n)		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous	Delayed	Relative risk (RR (95% CI))	Absolute	Quality
Need for repeat misoprostol												
1	RCTs	Serious*†	No serious inconsistency	No serious indirectness	Very serious‡	None	2/40 (5%)	1/40 (2.5%)	2.00 (0.19 to 21.18)	25 more per 1000 (from 20 fewer to 505 more)		Very low
Time to onset of bleeding (after misoprostol; hours)												
1	RCTs	Serious*	No serious inconsistency	No serious indirectness	No serious imprecision§	None	Median (range) 3.7 (0–74; n=554)	Median (range) 2 (–23–24; n=546)	NE¶	NE¶		Moderate
Time to onset of bleeding (after misoprostol; hours)												
1	RCTs	Very serious*†	No serious inconsistency	No serious indirectness	Serious**	None	40	40	NE	MD 0.74 higher (0.07 to 1.41 higher)		Very low
Time to onset of cramping (after misoprostol; hours)												
1	RCTs	Serious*	No serious inconsistency	No serious indirectness	No serious imprecision§	None	Median (range) 2.5 (0–143; n=554)	Median (range) 1.7 (–24–115; n=546)	NE¶	NE¶		Moderate
Incomplete abortion with the need for surgical intervention												
3	RCTs	Serious††	No serious inconsistency	No serious indirectness	Very serious‡	None	29/694 (4.2%)	22/686 (3.2%)	1.30 (0.76 to 2.25)	10 more per 1000 (from 8 fewer to 40 more)		Very low

*Unblinded study.

†Unclear adequacy of allocation concealment.

‡The CI crosses 0.8 and 1.25.

§No minimal important difference available for this outcome as it is only reported as medians and ranges. N>400.

¶Cannot be calculated as the study only reports medians and ranges (not means and SDs) which were statistically significantly different ($p<0.001$; Mann-Whitney U-test).

**Minimal important difference boundaries –0.62 and 0.62 (–/+1.24 * 0.5); clinically important effect=1.24*0.5=0.62 or above or –0.62 or below; the CI crossed one minimal important difference threshold.

††Unclear randomisation sequence generation and/or allocation concealment adequacy in two of the three studies. All the studies were unblinded.

MD, mean difference; NE, not estimable; RCT, randomised controlled trial; RR, relative risk.

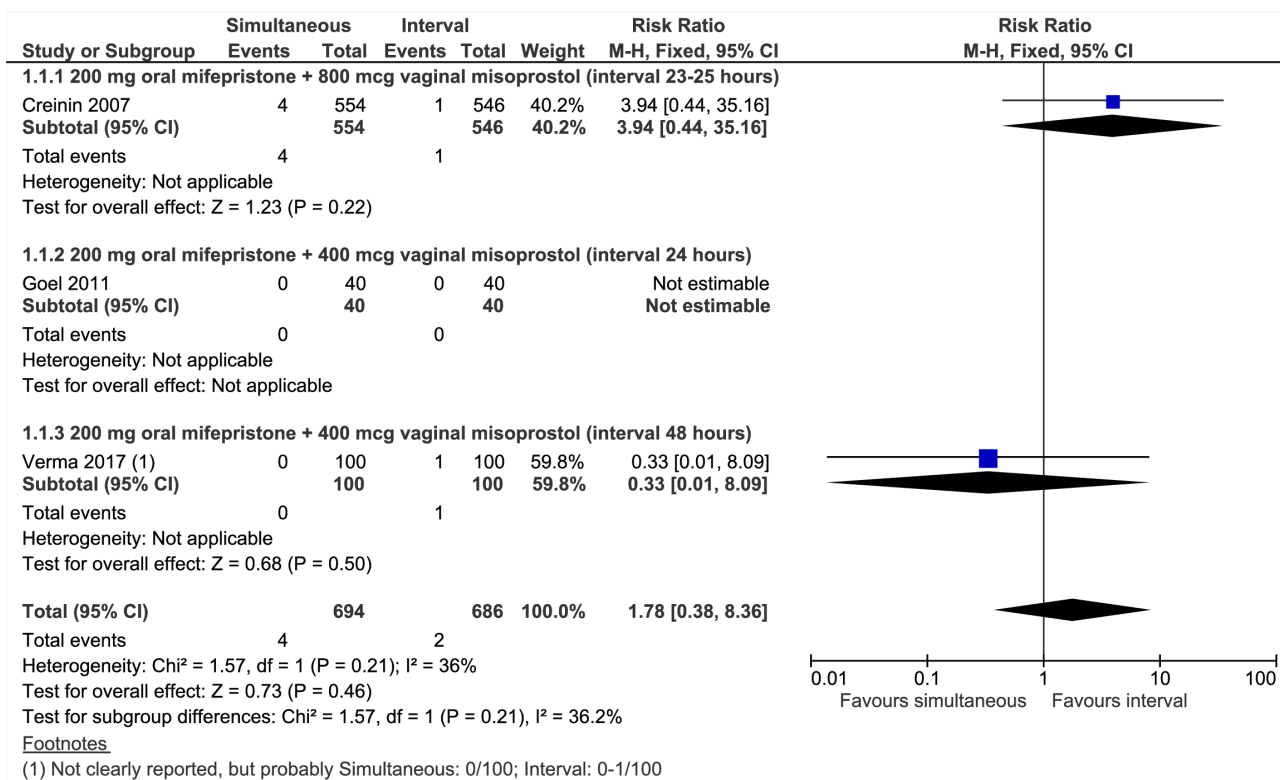


Figure 1 Ongoing pregnancy. CI, confidence interval; M-H, Mantel-Haenszel.

Quality of the evidence

The GRADE system was used to rate the quality of the evidence for each outcome using the GRADEprofiler Guideline Development Tool software,¹² and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*.¹⁰

For a result to be considered clinically significant, a minimal important difference (ie, effect size) between the intervention groups was defined as a statistically significant mean difference (MD) ≥ 0.5 times the SD of the control group for continuous outcomes and a statistically significant relative risk (RR) > 1.25 or < 0.8 for the dichotomous outcomes (ie, default GRADE values) apart from ‘haemorrhage requiring transfusion or ≥ 500 mL blood loss’, where simple statistical significance was also considered clinically significant due to the severity of this outcome. Imprecision was therefore present if the 95% CI of the MD crossed the ± 0.5 SD boundaries or if the 95% CI of the RR crossed 0.8 and/or 1.25 for any of the outcomes apart from ‘haemorrhage requiring transfusion or ≥ 500 mL blood loss’. For this outcome, the imprecision ratings were undertaken by using the optimum information size so that if the total event rate ≥ 300 , then the quality was not downgraded, if the event rate was 150–299, then the quality was downgraded by one level and if the event rate was < 150 , then the quality was downgraded by two levels. For continuous outcomes that were reported as medians and not means, imprecision was also rated using the optimum information size so

that if the total $n \geq 400$, then the quality was not downgraded, if the total $n = 200$ –399, then the quality was downgraded by one level and if the total $n < 200$, then the quality was downgraded by two levels.

The following outcomes were designated as critical outcomes ‘ongoing pregnancy’, ‘haemorrhage requiring transfusion or ≥ 500 mL blood loss’, and ‘patient satisfaction’, while ‘need for repeat misoprostol’, ‘time to onset of bleeding or cramping’, ‘total treatment time from mifepristone to expulsion’, and ‘incomplete abortion with the need for surgical intervention’ were designated as important outcomes. The reason for any decrease in quality rating has been justified in the footnotes of the summary of findings tables (table 1 and table 2).

Patient and public involvement

This systematic review was undertaken as part of the 2019 National Institute for Health and Care Excellence (NICE) guideline on abortion care,⁹ which was developed by a technical team at the National Guideline Alliance (NGA) based at the Royal College of Obstetricians and Gynaecologists (RCOG), and a guideline committee recruited specifically for this purpose. The guideline committee comprised a mix of clinical experts, commissioners and patient members, who collaboratively decided on the focus and specific parameters of the clinical question under consideration. Both the guideline scope and the draft guideline itself were also subject to public consultation prior

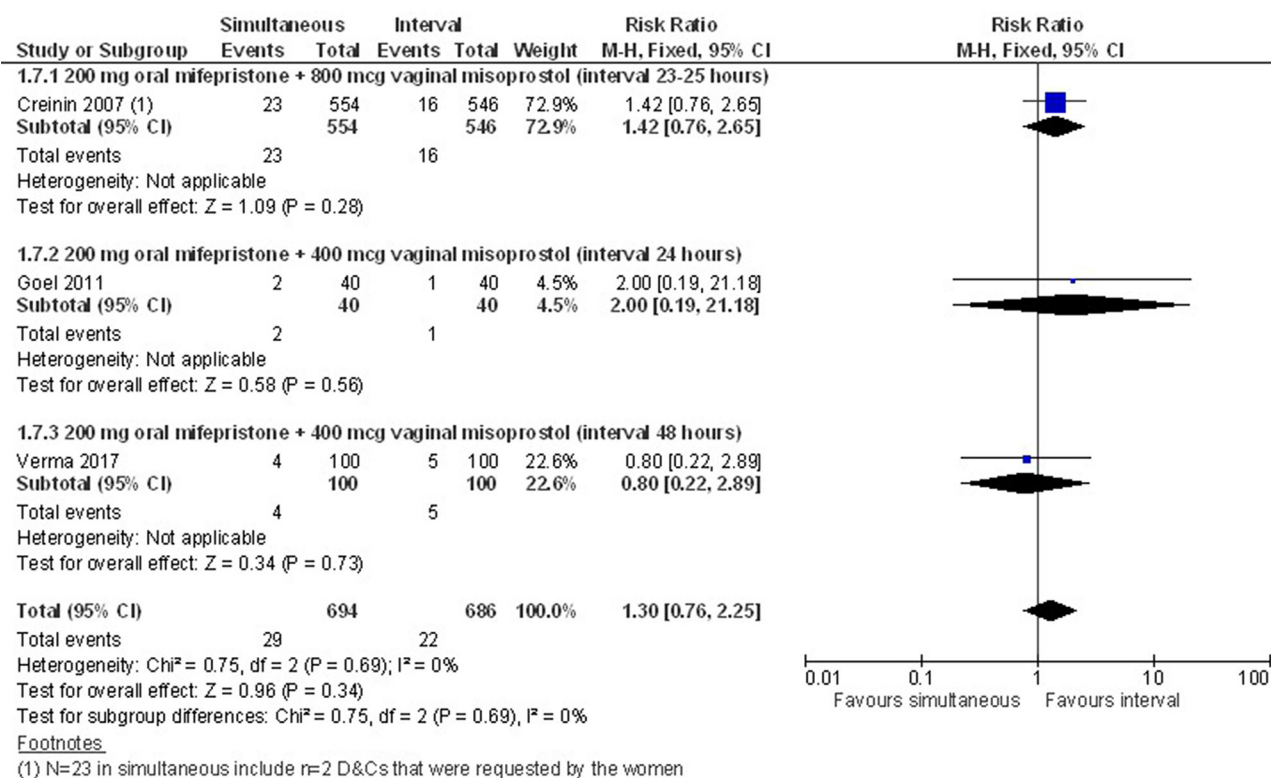


Figure 2 Incomplete abortion with the need for surgical intervention. CI, confidence interval; D&C, dilation & curettage; M-H, Mantel-Haenszel.

to being finalised. During both consultations any organisation registering as a stakeholder could submit comments, which the NGA/guideline committee took into account in the final versions of both the scope and guideline.

RESULTS

Study selection

The search of all the databases identified 569 possibly relevant papers of which 544 papers were excluded based on title/abstract and 25 papers were obtained for full-text review. Subsequently, 22 of these 25 papers were excluded as they did not meet the inclusion criteria (see also online supplementary table S1 for detailed exclusion reasons) and three studies were included in this review.

Study characteristics

All three studies included a total of 1280 women undergoing abortions of pregnancies up to 7³ or 9^{2,4} weeks' gestation, and used 200 mg mifepristone followed by either 400^{3,4} or 800² µg vaginal misoprostol, either within 15 min (simultaneous administration) or after an interval of 23–25^{2,3} or 48⁴ hours (interval administration). Two of the three studies were conducted in India^{3,4} with the third study undertaken in the USA.² Online supplementary table S2 provides a detailed description and assessment of each study.

Risk of bias of included studies

All the studies were unblinded which puts the results at risk of performance bias and detection bias to the extent that the outcomes were subjective. In two of the studies it was unclear whether allocation concealment was adequate,^{3,4} with the same concern being an issue for the randomisation method in one of those studies.⁴ Finally, one of the studies was at high risk of selective reporting bias with a number of stated outcomes not reported.⁴ All three studies were at low risk of attrition bias for all reported outcomes apart from patient satisfaction in the Creinin *et al* study, which was at high risk of attrition bias with data missing for 10% of the population in each intervention group.²

Synthesis of results

Meta-analyses showed that the rates of 'ongoing pregnancy' (RR 1.78, 95% CI 0.38 to 8.36; [figure 1](#) and [table 1](#)) and 'incomplete abortion with the need for surgical intervention' (RR 1.30, 95% CI 0.76 to 2.25; [figure 2](#) and [table 2](#)) did not differ clinically significantly between women whose medical abortion was initiated by simultaneous or interval administration of mifepristone and misoprostol. In the three studies, there were only four cases of 'haemorrhage requiring transfusion or ≥500 mL blood loss' and these were all observed in the interval group in the Creinin *et al* study,² and this difference was also not clinically significant between the intervention groups (RR 0.11, 95% CI 0.01 to 2.03; [table 1](#)).

The following outcomes could not be meta-analysed either because they were only reported by one of the included studies or because they were reported differently by the studies: patients' satisfaction, 'need for repeat misoprostol', 'time to onset of bleeding or cramping' and 'total treatment time'. Of these outcomes, 'need for repeat misoprostol' (RR 2.00, 95% CI 0.19 to 21.18; [table 2](#))³ and patient satisfaction were also not found to differ clinically significantly between the simultaneous and interval groups whether patient satisfaction was measured as "Would choose same method again" (RR 0.99, 95% CI 0.95 to 1.03; [table 1](#)),² "Would recommend to friend" (RR 1.00, 95% CI 0.97 to 1.03; [table 1](#))² or "Satisfied with procedure and would like to use this method again" (RR 1.03, 95% CI 0.94 to 1.12; [table 1](#)).³ Goel *et al* found that time to onset of bleeding after misoprostol administration was clinically significantly longer after simultaneous than interval administration (MD 0.74, 95% CI 0.07 to 1.41; [table 2](#)).³ Creinin *et al* also found that the median time to onset of bleeding after misoprostol administration was statistically significantly longer after simultaneous compared with interval administration of mifepristone and misoprostol and this was also the case for the median time to onset of cramping ([table 2](#)).²

'Total treatment time' was not reported by any of the studies, but Goel *et al*³ reported induction-to-abortion interval from misoprostol administration, which was 6.5 (SD 1.48) hours for the simultaneous group and 5.95 (SD 1.81) hours for the interval group ($p=0.13$).

The GRADE quality of evidence for the reported outcomes was very low to moderate, mainly due to the studies being unblinded and at risk of selection bias in two cases as well as the low event rates of many of the outcomes, and therefore very serious imprecision ([tables 1 and 2](#)).

DISCUSSION

Main findings

Overall, the results showed that simultaneous administration of mifepristone and misoprostol was not associated with clinically significantly different rates of 'ongoing pregnancy', 'haemorrhage requiring transfusion or ≥ 500 mL blood loss', 'patient satisfaction', 'need for repeat misoprostol' and 'incomplete abortion with the need for surgical intervention' compared with interval administration of mifepristone and misoprostol. However, simultaneous administration was associated with longer time to onset of bleeding and cramping. None of the studies directly reported our other target outcome of total treatment time or included women undergoing abortion of pregnancies between 9 and 10 weeks' gestation. The GRADE quality of evidence for all the reported outcomes was very low to moderate.

Strengths and limitations

From a process point of view, it is a clear strength of this study that the research question was selected due to variation in practice in this area. In addition, although there is guidance from the World Health Organisation (WHO) on medical management of abortion,¹³ there is a recognised need for guidance that is specifically applicable to the high income setting. Furthermore, the existing evidence base was examined in a systematic review using the well-established methods of the Cochrane Collaboration¹⁰ by experienced systematic reviewers within a long-standing guideline development framework with robust processes.¹⁴ However, the Cochrane Collaboration promotes the practice of two authors independently undertaking a number of the tasks associated with conducting a systematic review, such as dual sifting of the search and dual data extraction and bias appraisal. In this systematic review, due to resource limitations only one author performed all of these tasks formally, but this was accompanied by a more informal process of data extraction and bias assessment checking, through pre-existing knowledge of the evidence base by two of the other authors.

From a content point of view, it is clear that the evidence base for this research question is not large and is further compromised by the low event rates/number of participants for some of the outcomes, which does not allow the detection of more subtle differences between the interventions, including by gestational age, which we will now go on to discuss below. In addition, our comparator was interval administration of mifepristone and misoprostol and we were not able to examine dosing intervals of less than 23 hours. Moreover, two of the included studies used 400 μ g misoprostol whereas the third study used 800 μ g. Although both intervention groups within all of the studies received the same misoprostol dose, it is possible that misoprostol dose and interval interact. However, the paucity of data precludes us from examining this possibility.

Additional educational resources

- ▶ Kulier R, Kapp N, Gülmezoglu A, *et al*. Medical methods for first trimester abortion. *Cochrane Database Syst Rev* 2011;11:CD002855. DOI: 0.1002/14651858.CD002855.pub4.
- ▶ Raymond EG, Shannon C, Weaver MA, *et al*. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. *Contraception* 2013;87:26–37. doi: 10.1016/j.contraception.2012.06.011.
- ▶ British Pregnancy Advisory Service website: <https://www.bpas.org>

Interpretation

Although the results of this systematic review support the use of simultaneous mifepristone and misoprostol as an option for medical abortion up to 9⁺ weeks' gestation there was no evidence examining such abortions beyond this gestation, and for many of the outcomes the available evidence was not powered to detect any between-group differences. Moreover, the traditional interval regimens have a long, established practice while the evidence base for simultaneous regimens is weaker and contrasts somewhat with the authors' clinical experience, non-RCT literature and earlier meta-analyses of RCTs comparing the efficacy of medical abortion at intervals between mifepristone and misoprostol of >23 hours with shorter intervals of 6–8 hours that have reported reduced efficacy when the interval between the medication is shortened.¹⁵ The largest study to date on simultaneous regimens was conducted by Lohr and colleagues.⁵ This was a retrospective cohort study comparing simultaneous to interval regimens in the UK which included 28 901 women and had sufficient power to detect statistically significant differences between the two treatment groups that the smaller RCTs included in this systematic review could not. Importantly, the study was able to examine whether the success rate of the simultaneous regimen differed by gestation and found that the success rates of simultaneous administration were inversely proportional to gestation and increasingly inferior to routine interval administration as gestational age increased. However, while these differences were statistically significant, they remained small. For example, the surgical intervention rates for continuing pregnancy after simultaneous versus interval regimens at later gestations were 5% and 2.2%, respectively. Overall both simultaneous and interval regimens were demonstrated to be safe and effective. Of course, for some women a small increase in the risk of a continuing pregnancy with a simultaneous regimen might not be acceptable. It is important therefore that women who are considering choosing a simultaneous dosing regimen are provided with the necessary information to make an informed choice. This includes information on the importance of completing a follow-up programme to confirm the success of the medical abortion procedure.

There was evidence that bleeding and cramping started later with simultaneous than interval mifepristone and misoprostol. This may be an advantage for women who are taking both of the drugs in hospital or clinic before travelling home to complete the abortion because it gives the woman more time in which to return home before the onset of bleeding.¹⁶ This had been a significant factor in Great Britain prior to the change in regulations that now permit most women to take misoprostol at home. In addition, the total time from intake of mifepristone to completion of abortion is shorter, and so some

women may prefer simultaneous mifepristone and misoprostol because of this. Moreover, given that there were no other significant differences demonstrated by the simultaneous regimens, women can be reassured that if they are unable to wait for 24 hours to take misoprostol that the combination of drugs remains safe and effective even if taken at the same time as mifepristone.

CONCLUSIONS

On the basis of this evidence and the clinical experience of the guideline committee recruited to develop the 2019 NICE guideline on abortion care,⁹ the committee therefore agreed the following two clinical recommendations for women who have made a decision to proceed with an abortion:

1. Offer interval treatment (usually 24 to 48 hours) with mifepristone and misoprostol to women who are having a medical abortion up to and including 10⁺ weeks' gestation.
2. For women who are having a medical abortion up to and including 9⁺ weeks' gestation, give them the choice of having mifepristone and misoprostol at the same time, but explain that:
 - the risk of ongoing pregnancy may be higher, and it may increase with gestation.
 - it may take longer for the bleeding and cramping to start.
 - it is important for them to complete the same follow-up programme that is recommended for all medical abortions up to and including 10⁺ weeks (see recommendations 1.14.1 and 1.14.2 (Recommendation 1.14.1: For women who have had a medical abortion up to and including 10⁺ weeks' gestation with expulsion at home, offer the choice of self-assessment, including remote assessment (for example, telephone or text messaging), as an alternative to clinic follow-up. Recommendation 1.14.2: Provide women with a low-sensitivity or multi-level urine pregnancy test to exclude an ongoing pregnancy)).⁹

As simultaneous administration of mifepristone and misoprostol is not routinely offered in the UK these recommendations will result in changes to practice, but are unlikely to have a significant resource impact. Any net effect is likely to be a cost saving due to fewer visits being required for women receiving simultaneous administration compared with interval administration of mifepristone and misoprostol. However, if the complication rate of simultaneous administration is higher as suggested in the large retrospective study by Lohr *et al*,⁵ then it could result in additional costs for the National Health Service that could negate any other saving.

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Contributors SC, JL, EH and MSH conceived and designed the review and wrote the protocol. EH devised and undertook the search strategy. MSH screened the search results, performed the data extraction and 'risk of bias' assessment of the included studies, and the overall GRADE ratings. MSH devised and performed the analysis strategy. JL and SC interpreted the results. SC, MSH, EH and JL wrote the first draft of different sections of the full review. All the authors critically revised the first draft of the review and approved the final version.

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Table S1 Excluded studies with exclusion reasons

Study	Reason for Exclusion
Aubeny,E., Chatellier,G., A randomized comparison of mifepristone and self-administered oral or vaginal misoprostol for early abortion, <i>European Journal of Contraception and Reproductive Health Care</i> , 5, 171-176, 2000	Comparison not in PICO
Chen, M. J., Creinin, M. D., Mifepristone With Buccal Misoprostol for Medical Abortion: A Systematic Review, <i>Obstetrics & Gynecology</i> Obstet Gynecol, 126, 12-21, 2015	Systematic review only including studies with at least 24 hours between mifepristone and misoprostol (comparison not in PICO)
Creinin, Md, Schreiber, Ca, Bednarek, P, Lintu, H, Wagner, Ms, Meyn, L, A multicenter randomized equivalence trial of mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion through 63 days gestation (abstract), <i>Contraception</i> , 74, 178, 2006	Abstract of included full-text study (Creinin 2007)
El-Refaey, H., Rajasekar, D., Abdalla, M., Calder, L., Templeton, A., Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol, <i>New England Journal of Medicine</i> , 332, 983-987, 1995	Comparison not in PICO
Garg, G., Takkar, N., Sehgal, A., Buccal Versus Vaginal Misoprostol Administration for the Induction of First and Second Trimester Abortions, 65, 111-116, 2015	Comparison not in PICO
Iyengar, K., Klingberg-Allvin, M., Iyengar, S. D., Paul, M., Essen, B., Gemzell-Danielsson, K., Home use of misoprostol for early medical abortion in a low resource setting: Secondary analysis of a randomized controlled trial, <i>Acta obstetricia ET gynecologica scandinavica</i> , 95, 173-181, 2016	Comparison not in PICO
Jing, X, Weng, L, A study on the optimal regimen of mifepristone with prostaglandin for termination of early pregnancy, 30, 38-41, 1995	Comparisons not in PICO
Kahn,J.G., Becker,B.J., MacIsaac,L., Amory,J.K., Neuhaus,J., Olkin,I., Creinin,M.D., The efficacy of medical abortion: A meta-analysis, <i>Contraception</i> , 61, 29-40, 2000	Systematic review, comparison not in PICO
Kapp, N., Baldwin, M. K., Rodriguez, M. I., Efficacy of medical abortion prior to 6 gestational weeks: a systematic review, 97, 90-99, 2018	Systematic review (included studies checked for relevance): Comparison/analyses not in PICO
Kapp, N., et al. (2019). "Medical abortion in the late first trimester: a systematic review."	Systematic review (included studies

Study	Reason for Exclusion
Contraception 99(2): 77-86.	checked for relevance)
Li, Y. T., et al. (2008). Efficacy of simultaneous use of mifepristone and misoprostol for early abortion. International journal of gynaecology and obstetrics 101(3): 301	Non-comparative study
Ngo, T. D., Park, M. H., Shakur, H., Free, C., Comparative effectiveness, safety and acceptability of medical abortion at home and in a clinic: a systematic review, Bulletin of the world health organization, 89, 360-70, 2011	Systematic review (checked for relevant studies); comparison not in PICO
Pullen, R., Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: A randomised factorial controlled equivalence trial, 35, 150, 2009	Review of a study which only included comparisons not in PICO
Raymond, E. G., Shannon, C., Weaver, M. A., Winikoff, B., First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review, Contraception, 87, 26-37, 2013	Systematic review; focus on medical abortion as a whole and analyses not in PICO
Reeves, M. F., Monmaney, J. A., Creinin, M. D., Predictors of uterine evacuation following early medical abortion with mifepristone and misoprostol, Contraception, 93, 119-25, 2016	Secondary analysis of data from two studies, one of which is relevant and already included (Creinin 2007)
Sang, G. W., Weng, L. J., Shao, Q. X., Du, M. K., Wu, X. Z., Lu, Y. L., Cheng, L. N., Termination of early pregnancy by two regimens of mifepristone with misoprostol and mifepristone with PG05 - A multicentre randomized clinical trial in China, 50, 501-510, 1994	Comparison not in PICO
Schaff, E., Evidence for shortening the time interval of prostaglandin after mifepristone for medical abortion, Contraception, 74, 42-44, 2006	(Semi-)Systematic review (included studies checked for relevance): Comparison not in PICO
Shrestha, A., Sedhai, L. B., A randomized trial of hospital vs home self administration of vaginal misoprostol for medical abortion, Kathmandu University Medical Journal, 12, 185-189, 2014	Comparison not in PICO
Tendler, R., Bornstein, J., Kais, M., Masri, I., Odeh, M., Early versus late misoprostol administration after mifepristone for medical abortion, Archives of Gynecology and Obstetrics, 292, 1051-1054, 2015	Comparison not in PICO (2-hour v 48-hour intervals)
Tsai, E. M., Yang, C. H., Lee, J. N., Medical abortion with mifepristone and misoprostol: A clinical trial in Taiwanese women, Journal of the Formosan Medical Association, 101, 277-282, 2002	Comparison not in PICO

Study	Reason for Exclusion
Wedisinghe, L., Elsandabesee, D., Flexible mifepristone and misoprostol administration interval for first-trimester medical termination, Contraception, 81, 269-74, 2010	Systematic review: Included studies checked for relevance, and only relevant study already included (Creinin 2007)
Zou, Y, Li, Y P, Gan, C P, Wu, L, Tong, L, Liang, Y, Li, T, Tang, Y, Mei, L, Yang, J, Liu, Y W, Evaluation of the effectiveness of mifepristone concomitant with misoprostol for medical abortion (Provisional abstract), Chinese Journal of Evidence-Based Medicine, 5, 619-631, 2005	Systematic review, checked for relevant trials, no new trials identified

PICO: Population, intervention, comparison, outcomes.

Table S2 Included studies

Study details	Participants	Interventions	Outcomes and Results	Comments
<p>Full citation Creinin, M. D., Schreiber, C. A., Bednarek, P., Lintu, H., Wagner, M. S., Meyn, L. A., Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion: A randomized controlled trial, Obstetrics and Gynecology, 109, 885-894, 2007</p> <p>Ref Id 801807</p> <p>Country/ies where the study was carried out USA</p> <p>Study type Randomised controlled trial</p>	<p>Sample size n=1128 randomised (n=567 simultaneous; n=561 delayed) n=1100 analysed (simultaneous: n = 554, n=1 and 12 withdrew consent and were lost to follow up, respectively; delayed: n = 546, n=1 and 14 withdrew consent and were lost to follow up, respectively).</p> <p>Characteristics Simultaneous (analysed): Mean (SD) age: 26 (6) years; mean (SD) gestational age: 50 (8) days; Gravidity 1/2/3/4/5 or more: n=161/111/100/67/115; parity 0/1/2/3 or more: n=246/147/88/73; prior elective abortion(s): n=234; prior elective medical abortion: n =56.</p> <p>Delayed (analysed): Mean (SD) age: 26 (6) years; mean (SD) gestational age: 51 (8) days; Gravidity 1/2/3/4/5 or</p>	<p>Simultaneous administration: 200 mg oral mifepristone followed by 800 mcg vaginal misoprostol within 15 minutes</p> <p>Delayed administration: 200 mg oral mifepristone followed by 800 mcg vaginal misoprostol 23-25 hours later.</p> <p>50 mcg intramuscular rh-immune globulin was given to Rh-negative women.</p> <p>Follow-up: 7 (\pm1), 14 (\pm2) and 35 days after mifepristone administration</p>	<p>Critical outcomes: Ongoing pregnancy rate: Simultaneous: 4/554; Delayed: 1/546</p> <p>Haemorrhage requiring transfusion or \geq 500ml of blood loss: Simultaneous: 0/554; Delayed: 4/546 (gestational ages were 50, 51, 57 and 63 days)</p> <p>Patient satisfaction (would recommend to friend): Simultaneous:512/545; Delayed: 504/536</p> <p>Patient satisfaction (would choose same method again): Simultaneous:480/545; Delayed: 477/536</p> <p>Important outcomes: Need for repeat misoprostol: Not reported</p> <p>Time to onset of cramping (after misoprostol administration; median,</p>	<p>Limitations Quality assessment: Risk of bias assessed using Cochrane risk of bias tool</p> <p>Random sequence generation: Low risk; computer-generated list.</p> <p>Allocation concealment: Low risk; sequentially numbered opaque envelopes.</p> <p>Blinding of participants and personnel: Unblinded; unclear risk as most reported outcomes are subjective outcomes to some extent, apart from ongoing pregnancy, which is low risk.</p> <p>Blinding of outcome assessment: Unblinded; unclear risk as most reported outcomes are subjective outcomes to</p>

Study details	Participants	Interventions	Outcomes and Results	Comments
<p>Aim of the study "to compare the efficacy, adverse effects, and acceptability of misoprostol 800 mcg vaginally administered simultaneously with, or 24 hours after, mifepristone 200 mg orally for abortion in women up to 63 days of gestation." (p. 885)</p> <p>Study dates April 2004 - May 2006</p> <p>Source of funding Anonymous foundation</p>	<p>more: n= 143/108/105/83/107; parity 0/1/2/3 or more: n=216/140/127/63; prior elective abortion(s): n=231; prior elective medical abortion: n =68.</p> <p>Inclusion criteria Healthy women requesting an elective abortion of an intrauterine pregnancy (with a visible gestational sac) \leq 63 days of gestation (on the day of mifepristone administration; according to vaginal ultrasonography), who were willing to comply with the visit schedule and to have a surgical abortion indicated, with access to a telephone.</p> <p>Exclusion criteria Women with any contraindication to mifepristone (including chronic systemic corticosteroid administration or adrenal disease) or misoprostol (including glaucoma, mitral stenosis,</p>		<p>range; hours): Simultaneous: 2.5 (0-143); Delayed: 1.7 (-24 – 115); p < 0.001</p> <p>Time to onset of bleeding (after misoprostol administration; median, range; hours): Simultaneous: 3.7 (0-74); Delayed: 2 (-23 – 24); p < 0.001</p> <p>Total treatment time from mifepristone to expulsion: Not reported</p> <p>Incomplete abortion with the need for surgical intervention: Simultaneous: 23*/554; Delayed: 16/546. Includes n=2 D&Cs that were requested by the women</p>	<p>some extent, apart from ongoing pregnancy, which is low risk..</p> <p>Attrition: Low risk, for all outcomes apart from patient satisfaction data from 545/567 (simultaneous) and 536/561 (delayed) included.</p> <p>Selective reporting: Low risk</p> <p>Other bias: None reported</p> <p>Other information</p>

Study details	Participants	Interventions	Outcomes and Results	Comments
	sickle cell anemia, poorly controlled seizure disorder, or known allergy to prostaglandin); haemoglobin level <10 g/dL; cardiovascular disease (including angina, valvular disease, arrhythmia, or cardiac failure); known coagulopathy/ receiving treatment with anticoagulants; pregnancy with an intrauterine device in utero; an ultrasound examination showing evidence of an early pregnancy failure; active cervicitis on examination; breastfeeding; or previous participation in the trial.			
Full citation Goel, A., Mittal, S., Taneja, B. K., Singal, N., Attri, S., Simultaneous administration of mifepristone and misoprostol for early termination of pregnancy: A randomized	Sample size N=92 were screened of whom n=80 were randomised, n=40 to each intervention group Characteristics Simultaneous: Mean (?SD?) age: 25.65 (2.41) years; mean (SD?) gestational age: 36.52 (3.03) days; parity primigravida/multigravida:	Simultaneous administration: 200 mg oral mifepristone followed by 400 mcg vaginal misoprostol simultaneously Delayed administration: 200 mg oral mifepristone followed by 400 mcg vaginal misoprostol 24 hours later.	Critical outcomes: Ongoing pregnancy rate: Simultaneous: 0/40; Delayed: 0/40 Haemorrhage requiring transfusion or ≥ 500ml of blood loss: Simultaneous: 0/40; Delayed: 0/40 Patient satisfaction (satisfied	Limitations Quality assessment: Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk; random number table Allocation concealment: Unclear risk;

Study details	Participants	Interventions	Outcomes and Results	Comments
<p>controlled trial, Archives of gynecology and obstetrics, 283, 1409-1413, 2011</p> <p>Ref Id 816019</p> <p>Country/ies where the study was carried out India</p> <p>Study type Randomised controlled trial</p> <p>Aim of the study " To compare the efficacy of different intervals of misoprostol administration (simultaneously vis-à-vis 24 h), after mifepristone, in women undergoing medical termination of</p>	<p>n=9/31; previous abortion: n=15.</p> <p>Delayed: Mean (?SD?) age: 24.92 (2.45) years; mean (SD?) gestational age: 35.3 (4.08) days; parity primigravida/multigravida: n=11/29; previous abortion: n=18.</p> <p>The treatment groups did not differ significantly on any of these characteristics.</p> <p>Inclusion criteria Healthy women requesting an elective abortion for a single intrauterine pregnancy ≤49 days of gestation</p> <p>Exclusion criteria Women with an intrauterine device in situ, a history of > 2 cesarean sections, history of allergy to prostaglandins, bronchial asthma, hypertension, coronary artery disease, arrhythmias, renal or hepatic dysfunction, chronic</p>	<p>50 mcg intramuscular rh-immune globulin was given to Rh-negative women.</p> <p>Follow-up: 24 hours and 14 days after mifepristone administration</p>	<p>with procedure and would like to use this method again): Simultaneous:39/40; Delayed: 38/40</p> <p>Important outcomes: Need for repeat misoprostol: Simultaneous: 2/40; Delayed: 1/40</p> <p>Time to onset of cramping: Not reported</p> <p>Time to onset of bleeding (after misoprostol administration; mean? SD?; the study says in days, but then it is much longer than the induction-to-abortion interval which is given in hours, so that's most likely a typo and this is in hours also): Simultaneous: 4.89 (1.79); Delayed: 4.15 (1.24); p = 0.09</p> <p>Total treatment time from mifepristone to expulsion (induction-to-abortion interval from misoprostol administration reported;</p>	<p>sequentially numbered sealed envelopes prepared by a person not linked to the study, but unclear if envelopes could be seen through by the recruiter ("Women were asked to open the next sequentially numbered sealed envelope and assigned to a group accordingly." p 1410)</p> <p>Blinding of participants and personnel: Unblinded; unclear risk for all outcomes as they are all subjective outcomes to some extent, apart from ongoing pregnancy, which is low risk.</p> <p>Blinding of outcome assessment: Unblinded; unclear risk for all outcomes as they are all subjective outcomes to some extent, apart from ongoing pregnancy, which is low risk.</p>

Study details	Participants	Interventions	Outcomes and Results	Comments
<p>pregnancy up to gestation of 49 days." (p. 1409)</p> <p>Study dates October 2009 – July 2010</p> <p>Source of funding Not reported</p>	<p>adrenal failure or on anticoagulants and corticosteroids.</p>		<p>hours): Simultaneous: 6.5 (1.48); Delayed: 5.95 (1.81); p = 0.13; add 24 hours to delayed group to get total treatment time, but SD not correct then</p> <p>Incomplete abortion with the need for surgical intervention: Simultaneous: 2/40; Delayed: 1/40</p>	<p>Attrition: Low risk, for all outcomes data are included for all 80 patients</p> <p>Selective reporting: Low risk</p> <p>Other bias: None reported</p> <p>Other information</p>
<p>Full citation Verma, M. L., Singh, U., Singh, N., Sankhwar, P. L., Qureshi, S., Efficacy of concurrent administration of mifepristone and misoprostol for termination of pregnancy, Human fertility, 20, 43-47, 2017</p> <p>Ref Id 816539</p>	<p>Sample size N = 1410 screened for inclusion with N = 200 randomised (ITT population N = 200 [Simultaneous: N = 100; Delayed: N = 100]; PP population: N = 178 [Simultaneous: N = 90, with 10 lost to follow up; Delayed: N = 88, with 8 lost to follow up and 4 discontinuing the protocol])</p> <p>Characteristics Simultaneous: Mean (2SD) age = 27.5 (7) years; parity 0/1/2/3: N = 10/64/16/10;</p>	<p>Simultaneous administration: 200 mg oral mifepristone followed by 400 mcg vaginal misoprostol</p> <p>Delayed administration: 200 mg oral mifepristone followed by 400 mcg vaginal misoprostol 48 hours later.</p> <p>Women who were Rhesus negative received an intramuscular injection of 100 mcg Rhesus immunoglobulin.</p>	<p>Critical outcomes: Ongoing pregnancy rate: Not clearly reported, but probably Simultaneous: 0/100; Delayed: 0-1/100</p> <p>Haemorrhage requiring transfusion or ≥ 500ml of blood loss: Simultaneous: 0/100; Delayed: 0/100</p> <p>Patient satisfaction: Not reported</p> <p>Important outcomes: Need for repeat misoprostol: Not reported</p>	<p>Limitations</p> <p>Quality assessment: Risk of bias assessed using Cochrane risk of bias tool</p> <p>Random sequence generation: Unclear risk; "The subjects recruited in the study were randomized in two groups using computer software." (p. 44).</p> <p>Allocation concealment: Unclear risk; no information reported other</p>

Study details	Participants	Interventions	Outcomes and Results	Comments
<p>Country/ies where the study was carried out India</p> <p>Study type Randomised controlled trial</p> <p>Aim of the study To compare simultaneous administration of 200 mg oral mifepristone and 800 mcg vaginal misoprostol with 200 mg oral mifepristone and 800 mcg vaginal misoprostol 48 hours later for medical abortion in women with an intrauterine pregnancy ≤ 63 days gestation.</p> <p>Study dates August 2010-</p>	<p>gestational age $\leq 8 / > 8 - \leq 10$ weeks: N = 90/10; previous abortions 1/2: N = 54/26 Delayed: Mean (2SD) age = 26.5 (6.8) years; parity 0/1/2/3: N = 6/52/24/18; gestational age $\leq 8 / > 8 - \leq 10$ weeks: N = 85/15; previous abortions 1/2: N = 40/30 The treatment groups did not differ significantly on any of these baseline characteristics.</p> <p>Inclusion criteria Women with an intrauterine pregnancy ≤ 63 days gestation who were willing to comply with the study schedule and to have a surgical abortion if indicated.</p> <p>Exclusion criteria Women with ectopic pregnancy; systemic steroid therapy; adrenal insufficiency; bronchial asthma; glaucoma; poorly controlled seizures; haemoglobin < 10 gm/dl; sickle cell anaemia; known</p>	<p>Follow-up: 14 days after mifepristone or misoprostol administration (unclear)</p>	<p>Time to onset of cramping or bleeding: Not reported</p> <p>Total treatment time from mifepristone to expulsion: Not reported</p> <p>Incomplete abortion with the need for surgical intervention: Simultaneous: 4/100; Delayed: 5/100</p>	<p>than that detailed above.</p> <p>Blinding of participants and personnel: Unblinded; low risk as all reported outcomes are objective outcomes.</p> <p>Blinding of outcome assessment: Unblinded; low risk as all reported outcomes are objective outcomes.</p> <p>Attrition: Low risk as all patients included in the reported analyses/outcomes, although only 200/1410 women screened were included.</p> <p>Selective reporting: High risk; pain, patient preference (between surgical and medical abortion if another was needed in the future) and some secondary outcomes (e.g., difference in</p>

Study details	Participants	Interventions	Outcomes and Results	Comments
August 2011 Source of funding Not reported	coagulopathy: rheumatic heart disease; patients on anticoagulants; pregnancy with intra uterine contraceptive device in utero; acute cervicitis on examination; or ultrasound demonstrating early pregnancy failure.			induction abortion interval) not reported Other bias: None reported Other information

Appendix S1 Search strategies

Database: Medline & Embase (Multifile)

#	Searches
1	exp abortion/ use emczd
2	exp pregnancy termination/ use emczd
3	exp Abortion, Induced/ use ppez
4	Abortion Applicants/ use ppez
5	exp Abortion, Spontaneous/ use ppez
6	exp Abortion, Criminal/ use ppez
7	Aborted fetus/ use ppez
8	fetus death/ use emczd
9	abortion.mp.
10	(abort\$ or postabort\$ or preabort\$).mp.
11	((f?etal\$ or f?etus\$ or gestat\$ or midtrimester\$ or pregnan\$ or prenatal\$ or pre natal\$ or trimester\$) and terminat\$).mp.
12	((f?etal\$ or f?etus\$) adj loss\$).mp.
13	((gestat\$ or midtrimester\$ or pregnan\$ or prenatal\$ or pre natal\$ or trimester\$) adj3 loss\$).mp.
14	((elective\$ or threaten\$ or voluntar\$) adj3 interrupt\$) and pregnan\$).mp.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	Mifepristone/ use ppez
17	mifepristone/ use emczd
18	(mifepriston\$ or mifeprex\$ or mifegyn\$ or ru-486\$ or ru486\$ or ru-38486\$ or ru38486\$).mp.
19	16 or 17 or 18
20	Misoprostol/ use ppez
21	misoprostol/ use emczd
22	(misoprostol\$ or cytotec\$ or arthrotec\$ or oxaprost\$ or cyprostol\$ or mibetec\$ or prostokos\$ or misotrol\$).mp.

#	Searches
23	20 or 21 or 22
24	15 and 19 and 23
25	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
26	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
27	meta-analysis/
28	meta-analysis as topic/
29	systematic review/
30	meta-analysis/
31	(meta analy* or metanaly* or metaanaly*).ti,ab.
32	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
33	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
34	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36	(search* adj4 literature).ab.
37	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
38	cochrane.jw.
39	((pool* or combined) adj2 (data or trials or studies or results)).ab.
40	letter/
41	editorial/
42	news/
43	exp historical article/
44	Anecdotes as Topic/

#	Searches
45	comment/
46	case report/
47	(letter or comment*).ti.
48	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49	randomized controlled trial/ or random*.ti,ab.
50	48 not 49
51	animals/ not humans/
52	exp Animals, Laboratory/
53	exp Animal Experimentation/
54	exp Models, Animal/
55	exp Rodentia/
56	(rat or rats or mouse or mice).ti.
57	50 or 51 or 52 or 53 or 54 or 55 or 56
58	letter.pt. or letter/
59	note.pt.
60	editorial.pt.
61	case report/ or case study/
62	(letter or comment*).ti.
63	58 or 59 or 60 or 61 or 62
64	randomized controlled trial/ or random*.ti,ab.
65	63 not 64
66	animal/ not human/
67	nonhuman/
68	exp Animal Experiment/
69	exp Experimental Animal/

#	Searches
70	animal model/
71	exp Rodent/
72	(rat or rats or mouse or mice).ti.
73	65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74	57 use ppez
75	73 use emczd
76	74 or 75
77	25 use ppez
78	26 use emczd
79	77 or 78
80	(or/27-28,31,33-38) use ppez
81	(or/29-32,34-39) use emczd
82	80 or 81
83	24 and 76
84	24 not 83
85	limit 84 to english language
86	limit 85 to yr="1985 -Current"
87	79 or 82
88	86 and 87

Database: Cochrane Library via Wiley Online

#	Searches
#1	MeSH descriptor: [Abortion, Induced] explode all trees
#2	MeSH descriptor: [Abortion Applicants] explode all trees
#3	MeSH descriptor: [Abortion, Spontaneous] explode all trees

#	Searches
#4	MeSH descriptor: [Abortion, Criminal] explode all trees
#5	MeSH descriptor: [Aborted Fetus] explode all trees
#6	"abortion":ti,ab,kw (Word variations have been searched)
#7	(abort* or postabort* or preabort*):ti,ab,kw (Word variations have been searched)
#8	((fetal* or fetus* or foetal* or foetus* or gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) and terminat*):ti,ab,kw (Word variations have been searched)
#9	((fetal* or fetus* or foetal* or foetus*) next loss*):ti,ab,kw (Word variations have been searched)
#10	((gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) near/3 loss*):ti,ab,kw (Word variations have been searched)
#11	((elective* or threaten* or voluntar*) near/3 interrupt*) and pregnan*):ti,ab,kw (Word variations have been searched)
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	MeSH descriptor: [Mifepristone] this term only
#14	(mifepriston* or mifeprex* or mifegyn* or ru-486* or ru486* or ru-38486* or ru38486*):ti,ab,kw (Word variations have been searched)
#15	#13 or #14
#16	MeSH descriptor: [Misoprostol] this term only
#17	(misoprostol* or cytotec* or arthrotec* or oxaprost* or cyprostol* or mibetec* or prostokos* or misotrol*):ti,ab,kw (Word variations have been searched)
#18	#16 or #17
#19	#12 and #15 and #18 Publication Year from 1985 to 2018