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 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.

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.

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^{+0} 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^{+0} 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 trials[10] 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 5.3[11] 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.

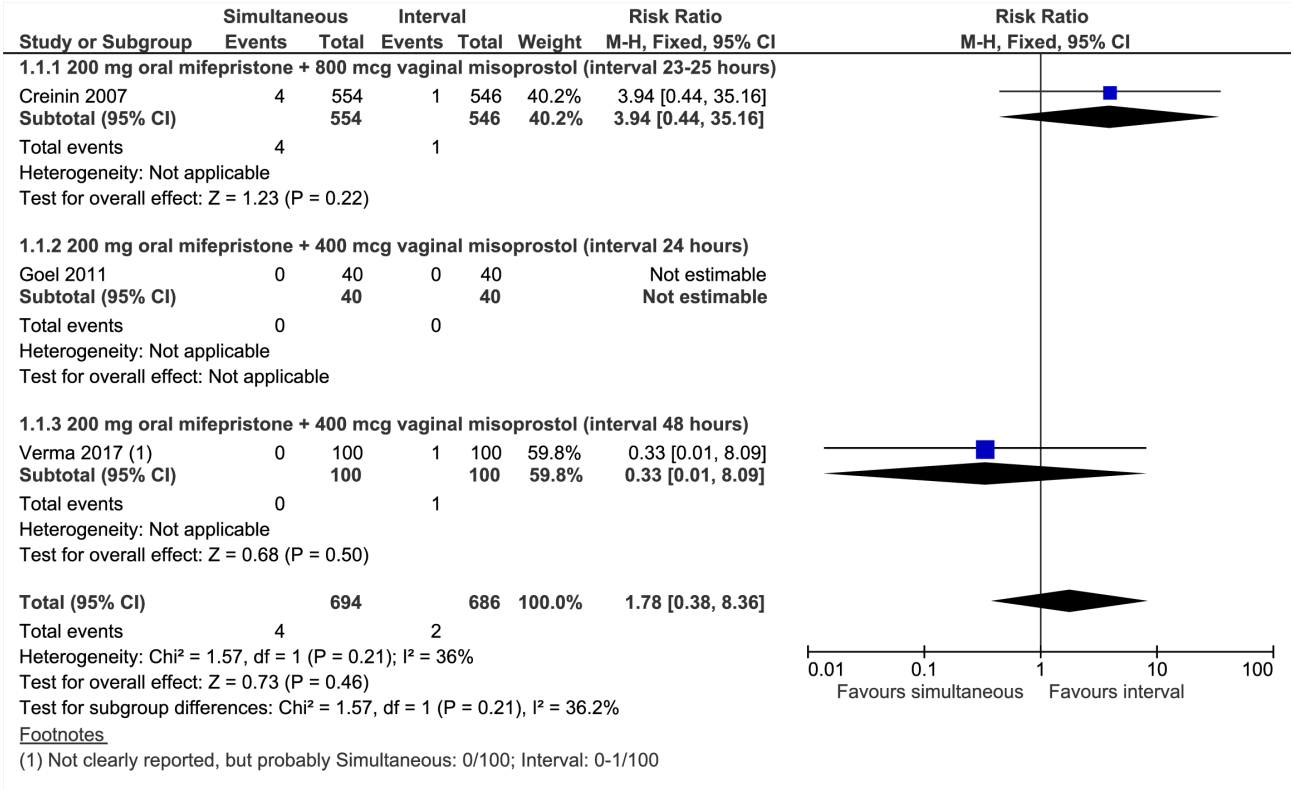

Figure 1 Ongoing pregnancy. CI, confidence interval; M-H, Mantel-Haenszel.

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≥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

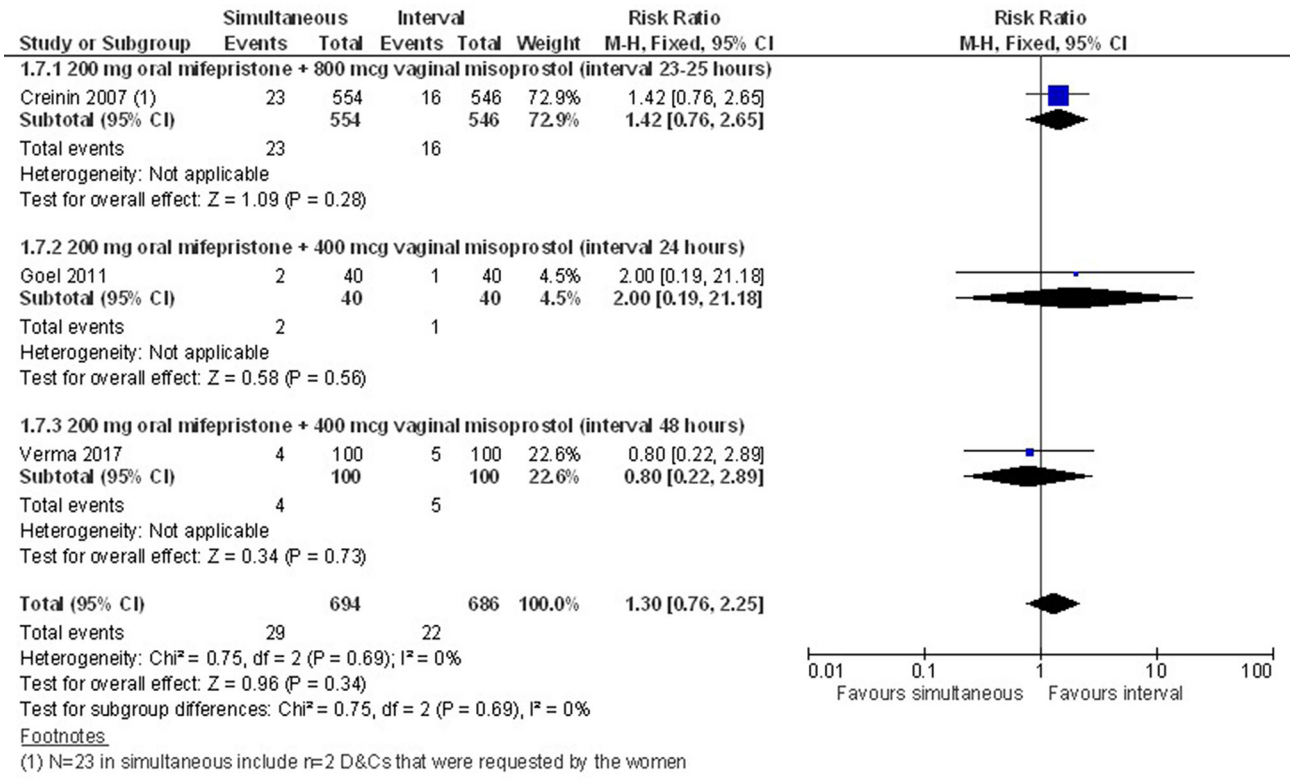

Figure 2 Incomplete abortion with the need for surgical intervention. CI, confidence interval; D&C, dilation & curettage; M-H, Mantel-Haenszel.

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 7[3] or 9[2 4] weeks' gestation, and used 200 mg mifepristone followed by either 400[3 4] or 800[2] µg vaginal misoprostol, either within 15 min (simultaneous administration) or after an interval of 23–25[2 3] or 48[4] 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 Collaboration[10] 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 µg misoprostol whereas the third study used 800 µg. 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^{+0} 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 misoprosotol 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^{+0} weeks' gestation.
2. For women who are having a medical abortion up to and including 9^{+0} 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^{+0} 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+0 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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