National Institute for Health and Care Excellence

Draft for Consultation

Termination of pregnancy

[H] Simultaneous versus delayed mifepristone + misoprostol administration for medical termination of pregnancy up to 10+0 weeks' gestation

NICE guideline <TBC>

Evidence reviews

April 2019

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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ISBN:

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Simultaneous versus delayed mifepristone + misoprostol administration for medical termination of pregnancy up to 10^{+0} weeks

Review question

For women who are having an early (up to 10^{+0} weeks' gestation) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

Introduction

The aim of this review is to determine the safety and acceptability of simultaneous administration of mifepristone and misoprostol administration compared with other time intervals up to 10^{+0} weeks' gestation.

Summary of the protocol

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women who are having a medical termination of pregnancy up to 10^{+0} weeks' gestation
Intervention	Simultaneous (within 15 minutes) administration of mifepristone and misoprostol.
Comparison	• Simultaneous administration versus <8 hour interval • Simultaneous administration versus 8 to 24 hour interval • Simultaneous administration versus >8 hour interval
Outcome	**Critical outcomes:** • Ongoing pregnancy rate • Haemorrhage requiring transfusion or ≥ 500ml of blood loss • Patient satisfaction **Important outcomes:** • Need for repeat misoprostol • Time to onset of cramping or bleeding • Total treatment time from mifepristone to expulsion • Incomplete abortion with the need for surgical intervention

For further details see the full review protocol in appendix A.

Clinical evidence

Included studies

Only studies conducted from 1985 onwards were considered for this review question, as mifepristone was made available in the UK in 1991 and evidence to support the use of mifepristone in practice is unlikely to be more than 5 years before its licensing in 1991.

Three RCTs were included in this evidence review. The RCTs compared medical termination of pregnancy up to 10^{+0} weeks' gestation using either simultaneous mifepristone and misoprostol administration or administration of misoprostol after a delay of 23-25 (Creinin

2007), 24 (Goel 2011) or 48 hours (Verma 2017), respectively, following mifepristone administration. The dose of oral mifepristone was 200 mg in all the studies, and all the studies used vaginal misoprostol, however, at different doses, with two of the studies using 400 mcg (Goel 2011; Verma 2011) and third study using 800 mcg (Creinin 2007). For this reason, the studies were analysed in the following two comparison groups: 1) Simultaneous oral mifepristone 200 mg and vaginal misoprostol 800 micrograms (mcg) versus vaginal misoprostol 800 mcg 23 to 25 hours after oral mifepristone 200mg, and 2) Simultaneous oral mifepristone 200 mg and vaginal misoprostol 400 mcg versus vaginal misoprostol 400 mcg 24 to 48 hours after oral mifepristone 200 mg.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review are presented in Table 2

Table 2: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes
Creinin 2007 RCT USA	n=1100 Healthy women requesting an elective termination of pregnancy of an intrauterine pregnancy (with a visible gestational sac) ≤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 termination of pregnancy indicated, with access to a telephone.	**Simultaneous administration:** 200mg oral mifepristone followed by 800micrograms (mcg) vaginal misoprostol within 15 minutes **Delayed administration:** 200mg oral mifepristone followed by 800mcg vaginal misoprostol 23 to 25 hours later.	• Ongoing pregnancy rate • Haemorrhage requiring transfusion or ≥500ml of blood loss • Patient satisfaction (would recommend to friend) • Patient satisfaction (would choose same method again) • Time to onset of cramping • Time to onset of bleeding • Incomplete abortion with the need for surgical intervention
Goel 2011 RCT	n=80 Healthy women	**Simultaneous administration:** 200mg oral mifepristone followed by	• Ongoing pregnancy rate • Haemorrhage requiring transfusion

Study and setting	Population	Intervention/ comparison	Outcomes
India	requesting an elective termination of pregnancy for a single intrauterine pregnancy ≤49 days of gestation.	400mcg vaginal misoprostol simultaneously **Delayed administration:** 200mg oral mifepristone followed by 400mcg vaginal misoprostol 24 hours later.	or ≥500ml of blood loss • Patient satisfaction (satisfied with procedure and would like to use this method again) • Need for repeat misoprostol • Time to onset of bleeding • Total treatment time from mifepristone to expulsion (induction-to-abortion interval from misoprostol administration reported) • Incomplete abortion with the need for surgical intervention
Verma 2017 RCT India	n=200 Women with an intrauterine pregnancy ≤63 days' gestation who were willing to comply with the study schedule and to have a surgical termination of pregnancy if indicated.	**Simultaneous administration:** 200mg oral mifepristone followed by 400mcg vaginal misoprostol **Delayed administration:** 200mg oral mifepristone followed by 400mcg vaginal misoprostol 48 hours later.	• Ongoing pregnancy rate • Haemorrhage requiring transfusion or ≥500ml of blood loss • Incomplete abortion with the need for surgical intervention

Mcg: micrograms; RCT: Randomised controlled trial

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical studies included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material 2 for details.

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Resource impact

Table 3: Costs of adverse events associated with medical termination of pregnancy

Resource	Unit costs	Source
Ongoing pregnancy	£464.03	Costs taken from bespoke economic modelling on this guideline. For full details of estimates please see Evidence Report K Appendix J and Evidence Report P Appendix J
Haemorrhage requiring transfusion or ≥500 ml blood loss	£178.54	
Incomplete abortion requiring surgical intervention	£464.03	
Repeat misoprostol 7 microgram per 1 hour	£93.00 per unit	BNF 75

Evidence statements

Comparison 1: Simultaneous oral mifepristone 200mg and vaginal misoprostol 800micrograms (mcg) versus vaginal misoprostol 800 mcg 23 to 25 hours after oral mifepristone 200mg

Critical outcomes

Ongoing pregnancy rate

RCT evidence did not detect a clinically important difference in the ongoing pregnancy rate between the simultaneous mifepristone and misoprostol group and the misoprostol 23 to 25 hours after mifepristone group (1 RCT, n=1100; RR = 3.94, 95% CI 0.44, 36.16; low quality); however there was uncertainty around the estimate.

Haemorrhage requiring transfusion or ≥500 ml blood loss

RCT evidence did not detect a clinically important difference in the rate of 'haemorrhage requiring transfusion or ≥500 ml blood loss' between the simultaneous mifepristone and misoprostol group and the misoprostol 23 to 25 hours after mifepristone group (1 RCT, n=1100; RR = 0.11, 95% CI 0.01, 2.03; very low quality); however there was uncertainty around the estimate

Patient satisfaction

RCT evidence showed no clinically important difference in patient satisfaction between the simultaneous mifepristone and misoprostol group and the misoprostol 23 to 25 hours after mifepristone group whether it was measured as "Would choose same method again" (RR = 0.99, 95% CI 0.95, 1.03) or "Would recommend to friend" (RR = 1, 95% CI 0.97, 1.03; 1 RCT, n=1100; moderate quality).

Important outcomes

Need for repeat misoprostol

No evidence was identified to inform this outcome.

Time to onset of bleeding or cramping (after misoprostol administration)

RCT evidence showed that the time to onset of bleeding and cramping *after misoprostol administration* were statistically[a] significantly longer in the simultaneous mifepristone and misoprostol group (Bleeding: median (range) = 3.7 (0-74) hours; Cramping: 2.5 (0-143) hours) compared with the misoprostol 23 to 25 hours after mifepristone group (Bleeding: median (range) = 2 (-23, 24) hours, p < 0.001; Cramping: 1.7 (-24, 115) hours, p < 0.001; 1 RCT, n=1100; moderate quality).

Total treatment time from mifepristone to expulsion

No evidence was identified to inform this outcome.

Incomplete abortion with the need for surgical intervention

RCT evidence did not detect a clinically important difference in the rate of incomplete abortion with the need for surgical intervention between the simultaneous mifepristone and misoprostol group and the misoprostol 23 to 25 hours after mifepristone group (1 RCT, n=1100; RR = 1.42, 95% CI 0.76, 2.65; very low quality); however there was uncertainty around the estimate.

Comparison 2: Simultaneous oral mifepristone 200mg and vaginal misoprostol 400mcg versus vaginal misoprostol 400mcg 24 to 48 hours after oral mifepristone 200mg

Critical outcomes

Ongoing pregnancy rate

RCT evidence did not detect a clinically important difference in the ongoing pregnancy rate between the simultaneous mifepristone and misoprostol group and the misoprostol 24 to 48 hours after mifepristone group (2 RCTs, n=280; RR = 0.33, 95% CI 0.01, 8.09; very low quality); however there was uncertainty around the estimate.

Haemorrhage requiring transfusion or ≥500 ml blood loss

RCT evidence reported no events of 'haemorrhage requiring transfusion or ≥ 500 ml blood loss' in either the simultaneous mifepristone and misoprostol group or the misoprostol 24 to 48 hours after mifepristone group; therefore differences between groups could not be estimated (2 RCTs, n=280; very low quality).

Patient satisfaction

RCT evidence showed no clinically important difference in patient satisfaction (measured as "Satisfied with procedure and would like to use this method again") between the simultaneous mifepristone and misoprostol group and the misoprostol 24 hours after mifepristone group (1 RCT, n=80; RR = 1.03, 95% CI 0.94, 1.12; low quality).

[a] Due to the use of medians for which there are no established or default GRADE MIDs it is unclear whether these differences are clinically important.

Important outcomes

Need for repeat misoprostol

RCT evidence did not detect a clinically important difference in the need for repeat misoprostol between the simultaneous mifepristone and misoprostol group and the misoprostol 24 hours after mifepristone group (1 RCT, n=80; RR = 2, 95% CI 0.19, 21.18; very low quality); however, there was uncertainty around the estimate.

Time to onset of bleeding or cramping (after misoprostol administration)

RCT evidence showed a longer clinically important difference in time to onset of bleeding *after misoprostol administration* in the simultaneous mifepristone and misoprostol group compared with the misoprostol 24 hours after mifepristone group (1 RCT, n=80; MD = 0.74 hours, 95% CI 0.07, 1.41; very low quality).

Total treatment time from mifepristone to expulsion

RCT evidence showed a shorter clinically important difference in the total treatment time from mifepristone to expulsion in the simultaneous mifepristone and misoprostol group compared with the misoprostol 24 hours after mifepristone group (1 RCT, n=80; MD = -23.45 hours, 95% CI -24.17, -22.73; low quality).

Incomplete abortion with the need for surgical intervention

RCT evidence did not detect a clinically important difference in the ongoing pregnancy rate did between the simultaneous mifepristone and misoprostol group and the misoprostol 24 to 48 hours after mifepristone group (2 RCTs, n=280; RR = 1, 95% CI 0.33, 3.03; very low quality); however, there was uncertainty around this estimate.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

At the start of the development of this guideline early medical abortion required two visits for a woman to the clinic in order to receive mifepristone (visit 1) and, after an interval of 1 to 2 days, misoprostol (visit 2). Simultaneous administration of these drugs could therefore improve service efficiency and flexibility, and patient experience and choice, however only if efficacy and serious side effects are broadly comparable with an interval administration schedule. The ongoing pregnancy rate was therefore selected as a critical outcome due to the impact on a women of both having to make the decision to undergo another termination procedure again for the same pregnancy as well as actually having to undergo the same procedure again. Subsequent changes to the law has now enabled women to take misoprostol at home and therefore women only need one visit to obtain both termination of pregnancy drugs. However, simultaneous administration of mifepristone and misoprostol could still potentially be appropriate under certain circumstances (see also "Other considerations" below) and the committee therefore still felt these outcomes were appropriate. The committee agreed that although haemorrhage requiring transfusion or ≥500 ml of blood loss is a rare outcome in women undergoing early medical termination of pregnancy, it should be prioritised as a critical outcome given the seriousness of the outcome. The committee also agreed to prioritise patient satisfaction as a critical outcome for decision making as termination of pregnancy is an area where women are known to have strong preferences. The need for repeat misoprostol and incomplete abortion with the need for surgical intervention were included as important outcomes due to the impact that needing a second appointment will have on both the woman and on available resources. Time to onset of cramping or bleeding and total treatment time from mifepristone to expulsion were

included as important outcomes because these variables are likely to influence which administration schedule a women might prefer depending on her circumstances, e.g., how she is getting home from the clinic, for example, if she is taking both of the drugs in clinic.

The quality of the evidence

The evidence in the pairwise comparisons was assessed using the GRADE methodology. The quality of the evidence across all outcomes ranged from very low to moderate quality and was most often downgraded due to design limitations because all the studies were unblinded and in two of the studies it was unclear whether the randomisation schedule or allocation concealment were adequate. The majority of the outcomes were also downgraded for imprecision due to low event rates.

Benefits and harms

The evidence showed that there were no clinically important differences in patient satisfaction between simultaneous and interval (23 to 48 hours) administration of mifepristone and misoprostol, whereas for ongoing pregnancy, haemorrhage requiring transfusion or ≥500 ml blood loss, need for repeat misoprostol, and incomplete abortion with the need for surgical intervention, it was unclear whether or not there was a clinically important difference. The evidence also showed a shorter clinically important difference in total treatment time from mifepristone to expulsion after simultaneous than interval administration of mifepristone and misoprostol, and that the time to onset of cramping or bleeding was clinically or statistically important longer after simultaneous compared to interval administration. It was unclear whether there was a clinically important difference in outcome between the treatment groups in both studies reporting this outcome because the way it was reported in one of the studies (as medians) precluded the possibility of meta-analysis. However, the evidence base was not of a high quality with the studies not powered to detect many of the more rare outcomes.

The committee did express concern that the findings from this review did not correlate with their own experience or that from other non-RCT literature and noted that traditional regimens have a long, established practice whilst the evidence base for simultaneous ones is weaker. The committee are aware of a significant paper comparing simultaneous to interval regimens in the UK which was not included in this review because it was a retrospective cohort study (Lohr 2018). Nevertheless it included sufficient numbers to be definitive (n=28,901) and its population appeared to be sufficiently similar to that in the included studies to infer that the results of the retrospective study would be applicable. The retrospective study had sufficient power to detect statistically significant differences between the 2 groups that the smaller RCTs could not. Whilst to an individual the differences are unlikely to be significant, given the numbers involved it could be relevant to the wider NHS. More importantly, the study defined a difference by gestation, with success rates of simultaneous administration inversely proportional to gestation and increasingly inferior to routine interval administration. These findings were in keeping with the experiences of the clinical experts. As a result of these differences, the committee agreed that they could not offer a strong recommendation to adopt simultaneous regimens, but that it should be available as an option for women who would prefer it.

Despite the limited evidence, the committee decided to prioritise other areas addressed by the guideline for future research and therefore made no research recommendations regarding the interval between mifepristone and misoprostol administration in women who are having a medical termination of a pregnancy up to 10^{+0} weeks' gestation.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee considered that there was unlikely to be a significant resource impact from the recommendations made. Any net effect was likely to be cost saving due to fewer visits being requiring for women receiving simultaneous administration compared to interval administration of mifepristone and misoprostol. However, if the complication rate of simultaneous administration is higher as suggested in the large retrospective study, whilst this is not clinically important, given the large numbers it could result in additional costs for the NHS that could negate any other saving.

Other considerations

The committee were aware that during the development of these guidelines the UK government approved the use of misoprostol at home. However, they still considered the question to be important, as that approval may not apply to the circumstances of all women and some may choose to have misoprostol administered in a clinic setting. Furthermore, the approval could be changed again during the lifetime of this guidance.

Given there were no significant differences demonstrated by the simultaneous regimens, the committee agreed that women could be reassured that if they do take misoprostol at home, that this lack of significant effect would suggest that they do not need to be concerned about timing the use of misoprostol with any precision.

References

Creinin 2007

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

Goel 2011

Goel, A., Mittal, S., Taneja, B. K., Singal, N., Attri, S., Simultaneous administration of mifepristone and misoprostol for early termination of pregnancy: A randomized controlled trial, Archives of gynecology and obstetrics, 283, 1409-1413, 2011

Lohr 2018

Lohr, P. A., Starling, J. E., Scott, J. G., and Aiken, A. R. A. Simultaneous Compared With Interval Medical Abortion Regimens Where Home Use Is Restricted. Obstetrics & Gynecology, 131, 635-41, 2018

Verma 2017

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

Appendices

Appendix A – Review protocols

Review protocol for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

Field (based on PRISMA-P	Content
Review question in SCOPE	For women who are having an early (up to 10 weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?
Review question in guideline	For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?
Type of review question	Intervention
Objective of the review	To determine the safety and acceptability of simultaneous administration of mifepristone and misoprostol administration compared with other time intervals up to 10^{+0} weeks' gestation
Eligibility criteria – population	Women who are having a medical termination of pregnancy up to 10^{+0} weeks' gestation Exclusions: - Studies with >10% of an indirect population
Eligibility criteria – intervention(s)	Simultaneous (within 15 minutes) administration of mifepristone and misoprostol.
Eligibility criteria – comparator(s)	1. Simultaneous administration versus <8 hour interval 2. Simultaneous administration versus 8 to 24 hour interval 3. Simultaneous administration versus >24 hour interval
Outcomes and prioritisation	**Critical outcomes:** • Ongoing pregnancy rate • Haemorrhage requiring transfusion or >500ml of blood loss • Patient satisfaction **Important outcomes:** • Need for repeat misoprostol • Time to onset of cramping or bleeding • Total treatment time from mifepristone to expulsion • Incomplete abortion with the need for surgical intervention
Eligibility criteria – study design	- Systematic reviews of RCTs

Field (based on PRISMA-P	Content
	- RCTs
Other inclusion exclusion criteria	Inclusion: - English-language
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of women, where possible: Medical conditions: - Complex pre-existing medical conditions - No complex pre-existing medical conditions Gestation: - <6^{+0} weeks - 6^{+1} weeks to 8^{+0} weeks - 8^{+1} weeks to 10^{+0} weeks Location of pregnancy expulsion: - Home - Healthcare setting - Not defined
Selection process – duplicate screening/selection/analysis	Dual weeding will not be performed for this question. Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual data extraction will not be performed for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations,
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Dates: from 1985 Studies conducted from 1985 onwards will be considered for this review question, as mifepristone was made available in the UK in 1991 and evidence to support the use of mifepristone in practice is unlikely to be more than 5 years before its licensing in 1991.
Identify if an update	Not an update
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B.

Field (based on PRISMA-P	Content
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists will be used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • RoBIS for systematic reviews • Cochrane risk of bias tool for RCTs The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Synthesis of data: Pairwise meta-analysis will be conducted where appropriate for all other outcomes. When meta-analysing continuous data, change scores will be pooled in preference to final scores. For details regarding inconsistency, please see the methods chapter Minimally important differences: For 'haemorrhage requiring transfusion or > 500ml of blood loss' statistical significance will be used. For all other outcomes, default values will be used: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD (of the control group) for continuous outcomes.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Professor Iain Cameron in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance will undertake systematic literature searches, appraise

Field (based on PRISMA-P	Content
	the evidence, conduct meta-analysis and cost-effectiveness analysis where appropriate, and draft the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

GRADE: Grading of Recommendations Assessment, Development and Evaluation; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NGA: National Guideline Alliance; RCT: randomised controlled trial

Appendix B – Literature search strategies

Literature search strategy for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

The search for this topic was last run on 3rd May 2018. It was decided not to undertake a re-run for this topic in November 2018 as this is not a fast moving evidence base and there were unlikely to be any new studies published which would affect the recommendations.

Database: Medline & Embase (Multifile)

Last searched on **Embase Classic+Embase** 1947 to 2018 May 02, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Date of last search: 3rd May 2018

#	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.
23	20 or 21 or 22

#	Searches
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/
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/

#	Searches
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/
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	remove duplicates from 86
88	79 or 82
89	87 and 88

Database: Cochrane Library via Wiley Online

Date of last search: 3rd May 2018

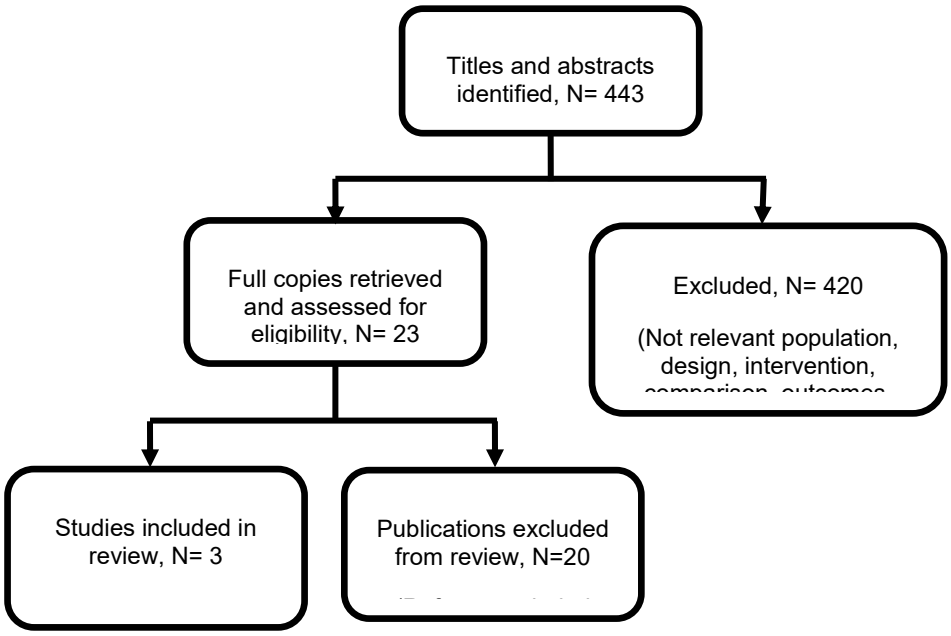
#	Searches
#1	MeSH descriptor: [Abortion, Induced] explode all trees
#2	MeSH descriptor: [Abortion Applicants] explode all trees
#3	MeSH descriptor: [Abortion, Spontaneous] explode all trees
#4	MeSH descriptor: [Abortion, Criminal] explode all trees
#5	MeSH descriptor: [Aborted Fetus] explode all trees
#6	"abortion":ti,ab,kw (Word variations have been searched)
#7	(abort* or postabort* or preabort*):ti,ab,kw (Word variations have been searched)

#	Searches
#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

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

Study details	Participants	Interventions	Outcomes and Results	Comments
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 **Ref Id** 801807 **Country/ies where the study was carried out** USA **Study type**	**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). **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 termination of pregnancy(s): n=234; prior elective medical termination of pregnancy: n =56. Delayed (analysed): Mean (SD) age: 26 (6) years; mean (SD) gestational age: 51 (8) days; Gravidity 1/2/3/4/5 or more: n=	**Simultaneous administration:** 200mg oral mifepristone followed by 800mcg vaginal misoprostol within 15 minutes. **Delayed administration:** 200mg oral mifepristone followed by 800mcg vaginal misoprostol 23 to 25 hours later. 50mcg intramuscular rh-immune globulin was given to Rh-negative women. **Follow-up:** 7 (±1), 14 (±2) and 35 days after mifepristone administration.	**Outcome: Ongoing pregnancy rate** Simultaneous: 4/554 Delayed: 1/546 **Outcome: Haemorrhage requiring transfusion or > 500ml of blood loss** Simultaneous: 0/554 Delayed: 4/546 (gestational ages were 50, 51, 57 and 63 days) **Outcome: Patient satisfaction** Would recommend to friend Simultaneous:512/545 Delayed: 504/536 Would choose same method again Simultaneous:480/545 Delayed: 477/536 **Outcome: Time to onset of cramping (after misoprostol administration; median, range; hours)** Simultaneous: 2.5 (0-143)	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk; computer-generated list. Allocation concealment: Low risk; sequentially numbered opaque envelopes. 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. Blinding of outcome assessment: Unblinded; unclear risk as most reported outcomes are subjective outcomes to some extent, apart from ongoing pregnancy, which is low risk.. Attrition: Low risk, for all outcomes apart from patient satisfaction data from 545/567

Study details	Participants	Interventions	Outcomes and Results	Comments
Randomised controlled trial **Aim of the study** "to compare the efficacy, adverse effects, and acceptability of misoprostol 800micrograms (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) **Study dates** April 2004 – May 2006 **Source of funding** Anonymous foundation	143/108/105/83/107; parity 0/1/2/3 or more: n=216/140/127/63; prior elective termination of pregnancy(s): n=231; prior elective medical termination of pregnancy: n =68. **Inclusion criteria** Healthy women requesting an elective termination of pregnancy of an intrauterine pregnancy (with a visible gestational sac) ≤ 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 termination of pregnancy indicated, with access to a telephone. **Exclusion criteria** Women with any contraindication to mifepristone (including chronic systemic corticosteroid administration or adrenal disease) or misoprostol (including glaucoma, mitral stenosis, sickle cell anaemia, poorly controlled seizure disorder, or known allergy to prostaglandin); haemoglobin level <10 g/dL; cardiovascular		Delayed: 1.7 (-24 – 115) p < 0.001 **Outcome: Time to onset of bleeding (after misoprostol administration; median, range; hours)** Simultaneous: 3.7 (0-74) Delayed: 2 (-23 – 24) p < 0.001 **Outcome: 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	(simultaneous) and 536/561 (delayed) included. Selective reporting: Low risk Other bias: None reported **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	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 controlled trial, Archives of gynecology and obstetrics, 283, 1409-1413, 2011 **Ref Id** 816019 **Country/ies where the study was carried out**	**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: n=9/31; previous termination of pregnancy: n=15. 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 termination of pregnancy: n=18.	**Simultaneous administration** 200mg oral mifepristone followed by 400mcg vaginal misoprostol simultaneously. **Delayed administration** 200mg oral mifepristone followed by 400mcg vaginal misoprostol 24 hours later. 50mcg intramuscular rh-immune globulin was given to Rh-negative women. **Follow-up** 24 hours and 14 days after mifepristone administration.	**Outcome: Ongoing pregnancy rate** Simultaneous: 0/40 Delayed: 0/40 **Outcome: Haemorrhage requiring transfusion or > 500ml of blood loss** Simultaneous: 0/40 Delayed: 0/40 **Outcome: Patient satisfaction (satisfied with procedure and would like to use this method again)** Simultaneous:39/40 Delayed: 38/40 **Outcome: Need for repeat misoprostol** Simultaneous: 2/40 Delayed: 1/40	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk; random number table Allocation concealment: Unclear risk; 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) Blinding of participants and personnel: Unblinded; unclear risk for all outcomes as they are all subjective outcomes to

Study details	Participants	Interventions	Outcomes and Results	Comments
India Study type **Randomised controlled trial** **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 pregnancy up to gestation of 49 days." (p. 1409) **Study dates** October 2009 – July 2010 **Source of funding** Not reported	The treatment groups did not differ significantly on any of these characteristics. **Inclusion criteria** Healthy women requesting an elective termination of pregnancy for a single intrauterine pregnancy ≤49 days of gestation **Exclusion criteria** Women with an intrauterine device in situ, a history of > 2 caesarean sections, history of allergy to prostaglandins, bronchial asthma, hypertension, coronary artery disease, arrhythmias, renal or hepatic dysfunction, chronic adrenal failure or on anticoagulants and corticosteroids.		**Outcome: 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 **Outcome: Total treatment time from mifepristone to expulsion (induction-to-abortion interval from misoprostol administration reported; 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 **Outcome: Incomplete abortion with the need for surgical intervention** Simultaneous: 2/40 Delayed: 1/40	some extent, apart from ongoing pregnancy, which is low risk. 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. Attrition: Low risk, for all outcomes data are included for all 80 women Selective reporting: Low risk Other bias: None reported **Other information** None
Full citation Verma, M. L., Singh, U., Singh, N., Sankhwar, P. L.,	**Sample size** N = 1410 screened for inclusion with N = 200 randomised (ITT population N = 200	**Simultaneous administration:**	**Outcome: Ongoing pregnancy rate** Simultaneous: 0/100 Delayed: 0-1/100	**Limitations** **Quality of study:**

Study details	Participants	Interventions	Outcomes and Results	Comments
Qureshi, S., Efficacy of concurrent administration of mifepristone and misoprostol for termination of pregnancy, Human fertility, 20, 43-47, 2017 **Ref Id** 816539 **Country/ies where the study was carried out** India **Study type** Randomised controlled trial **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	[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]) **Characteristics** Simultaneous: Mean (2SD) age = 27.5 (7) years; parity 0/1/2/3: N = 10/64/16/10; gestational age ≤8 / >8 - ≤10 weeks: N = 90/10; previous termination of pregnancy 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 ≤8 / >8 - ≤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. **Inclusion criteria** Women with an intrauterine pregnancy ≤ 63 days gestation who were willing to comply with the study schedule and to have a surgical termination of pregnancy if indicated. **Exclusion criteria**	200mg oral mifepristone followed by 400mcg vaginal misoprostol. **Delayed administration:** 200mg oral mifepristone followed by 400mcg vaginal misoprostol 48 hours later. Women who were Rhesus negative received an intramuscular injection of 100mcg Rhesus immunoglobulin. **Follow-up:** 14 days after mifepristone or misoprostol administration (unclear).	Not clearly reported, but probably **Outcome: Haemorrhage requiring transfusion or > 500ml of blood loss** Simultaneous: 0/100 Delayed: 0/100 **Outcome: Incomplete abortion with the need for surgical intervention** Simultaneous: 4/100 Delayed: 5/100	Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Unclear risk; "The subjects recruited in the study were randomized in two groups using computer software." (p. 44). Allocation concealment: Unclear risk; no information reported other than that detailed above. Blinding of participants and personnel: Unblinded; low risk as all reported outcomes are objective outcomes. Blinding of outcome assessment: Unblinded; low risk as all reported outcomes are objective outcomes. Attrition: Low risk as all patients included in the reported analyses/outcomes, although only 200/1410 women screened were included. Selective reporting: High risk; pain, patient preference (between surgical and medical termination of pregnancy if another was needed in the future) and some secondary outcomes (e.g., difference in induction abortion interval) not reported

Study details	Participants	Interventions	Outcomes and Results	Comments
medical abortion in women with an intrauterine pregnancy ≤ 63 days gestation. **Study dates** August 2010 – August 2011 **Source of funding** Not reported	Women with ectopic pregnancy; systemic steroid therapy; adrenal insufficiency; bronchial asthma; glaucoma; poorly controlled seizures; haemoglobin < 10 gm/dl; sickle cell anaemia; known coagulopathy: rheumatic heart disease; women on anticoagulants; pregnancy with intra uterine contraceptive device in utero; acute cervicitis on examination; or ultrasound demonstrating early pregnancy failure.			Other bias: None reported **Other information** None

D&C: dilatation & curettage; ITT: intention to treat; mcg: micrograms

Appendix E – Forest plots

Forest plots for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

Figure 1. Ongoing pregnancy rate after simultaneous or delayed mifepristone and misoprostol administration

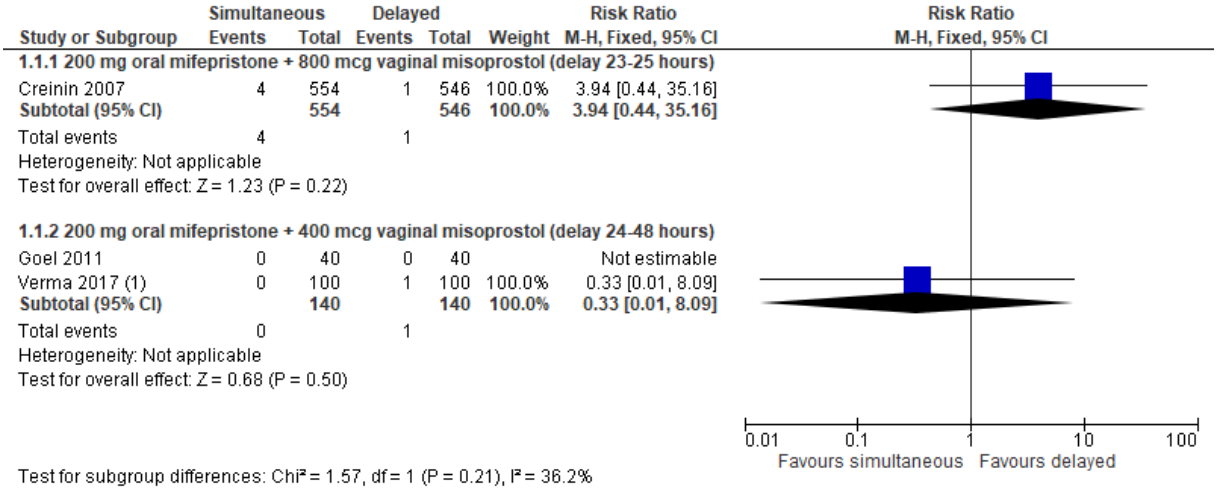


Figure 2. Haemorrhage requiring transfusion or 500 ml blood loss or above after simultaneous or delayed mifepristone and misoprostol administration

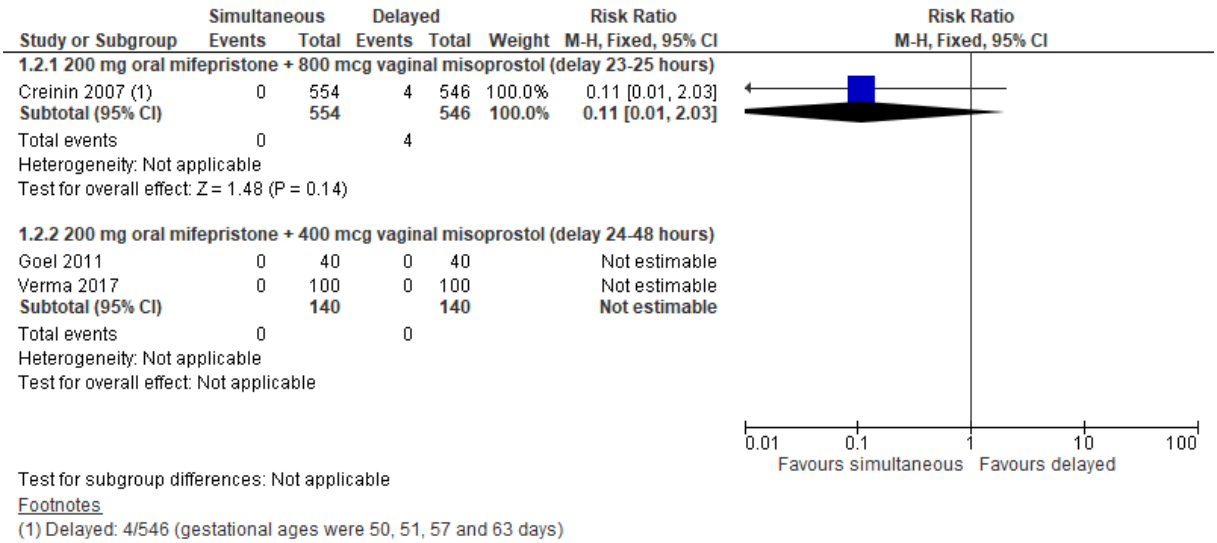
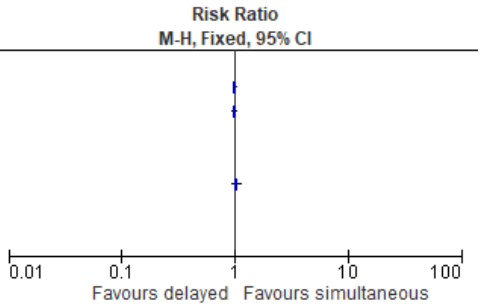


Figure 3. Patient satisfaction after simultaneous or delayed mifepristone and misoprostol administration

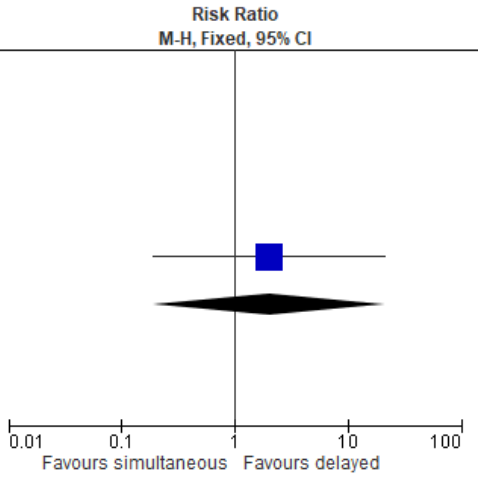
Study or Subgroup	Simultaneous Events	Simultaneous Total	Delayed Events	Delayed Total	Risk Ratio M-H, Fixed, 95% CI
1.3.1 200 mg oral mifepristone + 800 mcg vaginal misoprostol (delay 23-25 hours)					
Creinin 2007 (1)	512	545	504	536	1.00 [0.97, 1.03]
Creinin 2007 (2)	480	545	477	536	0.99 [0.95, 1.03]
1.3.2 200 mg oral mifepristone + 400 mcg vaginal misoprostol (delay 24-48 hours)					
Goel 2011 (3)	39	40	38	40	1.03 [0.94, 1.12]
Verma 2017 (4)	0	0	0	0	Not estimable



Footnotes
(1) 'Would recommend to friend'
(2) 'Would choose same method again'
(3) 'Satisfied with procedure and would like to use this method again'
(4) Not reported

Figure 4. Need for repeat misoprostol after simultaneous or delayed mifepristone and misoprostol administration

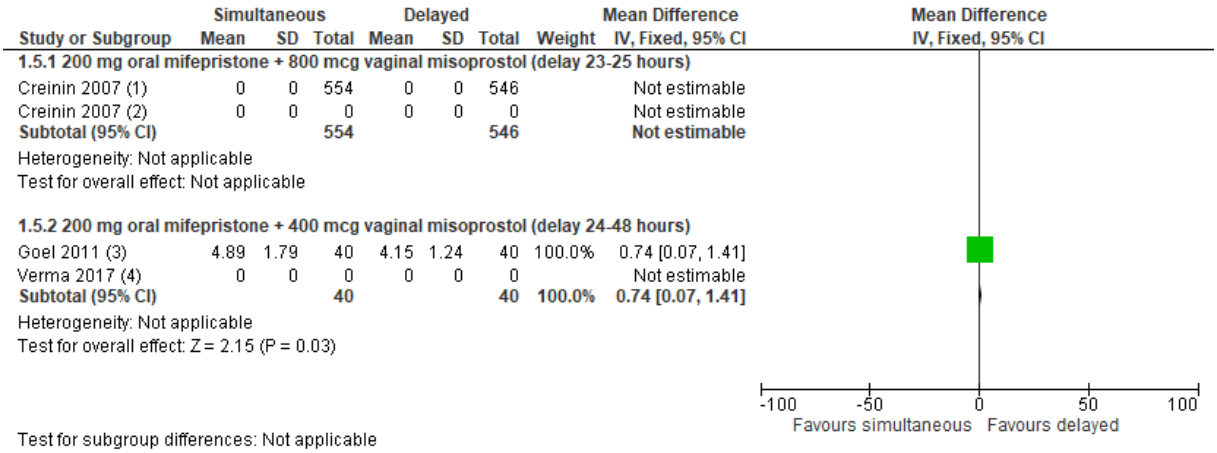
Study or Subgroup	Simultaneous Events	Simultaneous Total	Delayed Events	Delayed Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 200 mg oral mifepristone + 800 mcg vaginal misoprostol (delay 23-25 hours)						
Creinin 2007 (1)	0	0	0	0		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.4.2 200 mg oral mifepristone + 400 mcg vaginal misoprostol (delay 24-48 hours)						
Goel 2011	2	40	1	40	100.0%	2.00 [0.19, 21.18]
Verma 2017 (2)	0	0	0	0		Not estimable
Subtotal (95% CI)		**40**		**40**	**100.0%**	**2.00 [0.19, 21.18]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						



Test for subgroup differences: Not applicable

Footnotes
(1) Not reported
(2) Not reported

Figure 5. Time to onset of cramping or bleeding after simultaneous or delayed mifepristone and misoprostol administration



Foot notes (they have not all come out fully in the forest plot from Review Manager)

(1) Time to onset of cramping (after misoprostol administration) mean and SD not reported, but median (range; hours) was: Simultaneous: 2.5 (0-143); Delayed: 1.7 (-24 – 115); $p < 0.001$

(2) Time to onset of bleeding (after misoprostol administration) mean and SD not reported but median (range; hours) was: Simultaneous: 3.7 (0-74); Delayed: 2 (-23 – 24); $p < 0.001$

(3) Time to onset of bleeding (after misoprostol administration [cramping not reported]; 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

(4) Not reported

Figure 6. Total treatment time from mifepristone to expulsion after simultaneous or delayed mifepristone and misoprostol administration

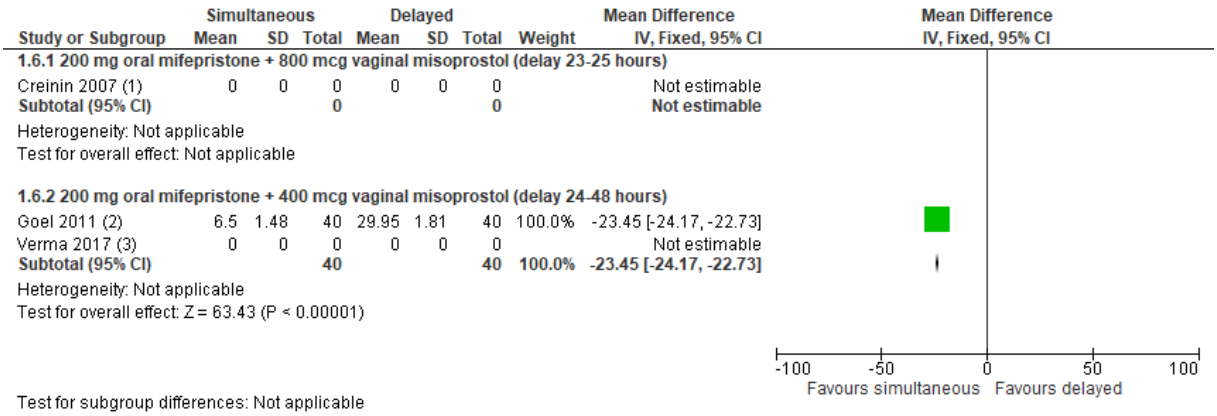
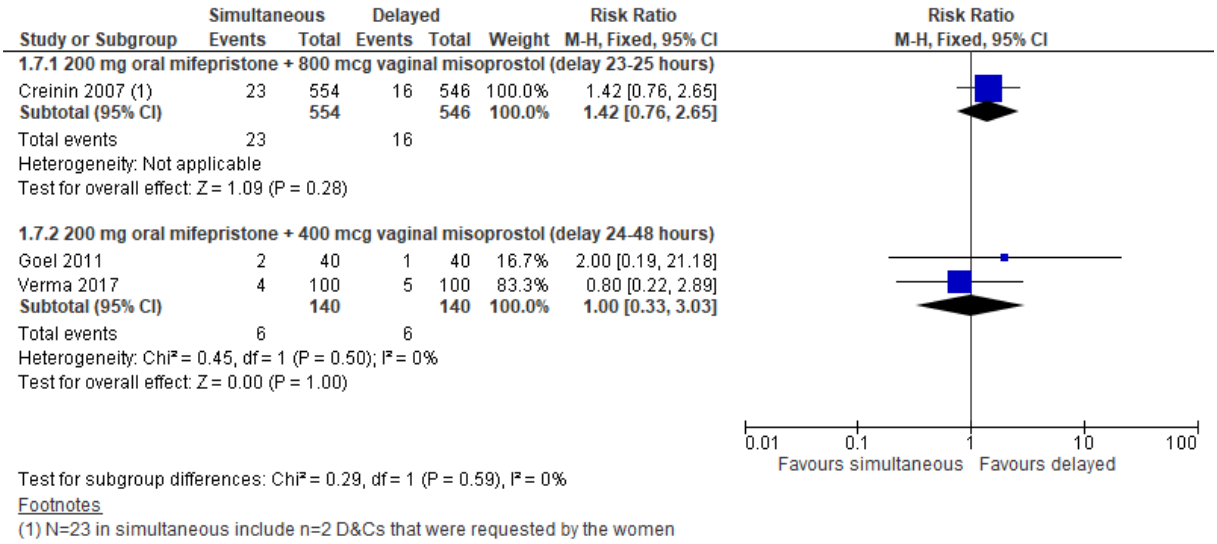


Figure 7. Incomplete abortion with the need for surgical intervention after simultaneous or delayed mifepristone and misoprostol administration



Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%

Footnotes

(1) N=23 in simultaneous include n=2 D&Cs that were requested by the women

Appendix F – GRADE tables

GRADE tables for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

Table 4: Clinical evidence profile: Comparison 1: Simultaneous oral mifepristone 200 mg and vaginal misoprostol 800 mcg versus vaginal misoprostol 800 mcg 23-25 hours after oral mifepristone 200 mg

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous	Delayed	Relative (95% CI)	Absolute	Quality	Importance
Ongoing pregnancy rate												
1 (Creinin 2007)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	4/554 (0.72%)	1/546 (0.18%)	RR 3.94 (0.44 to 35.16)	5 more per 1000 (from 1 fewer to 63 more)	LOW	CRITICAL
Haemorrhage requiring transfusion or 500 ml blood loss or above												
1 (Creinin 2007)	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	None	0/554 (0%)	4/546 (0.73%)	RR 0.11 (0.01 to 2.03)	7 fewer per 1000 (from 7 fewer to 8 more)	VERY LOW	CRITICAL
Patient satisfaction ("Would choose same method again")												
1 (Creinin 2007)	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	480/545 (88.1%)	477/536 (89%)	RR 0.99 (0.95 to 1.03)	9 fewer per 1000 (from 44 fewer to 27 more)	MODERATE	CRITICAL
Patient satisfaction ("Would recommend to friend")												
1 (Creinin 2007)	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	512/545 (93.9%)	504/536 (94%)	RR 1.00 (0.97 to 1.03)	0 fewer per 1000 (from 28 fewer to 28 more)	MODERATE	CRITICAL
Time to onset of bleeding (after misoprostol; hours; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Simultaneous**	**Delayed**	**Relative (95% CI)**	**Absolute**		
1 (Creinin 2007)	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision[4]	None	Median (range) 3.7 (0-74; n=554)	Median (range) 2 (-23 – 24; n=546)	Not estimable[5]	Not estimable[5]	MODERATE	IMPORTANT
Time to onset of cramping (after misoprostol; hours; Better indicated by lower values)												
1 (Creinin 2007)	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision[4]	None	Median (range) 2.5 (0-143; n=554)	Median (range) 1.7 (-24 – 115; n=546)	Not estimable[6]	Not estimable[6]	MODERATE	IMPORTANT
Incomplete abortion with the need for surgical intervention												
1 (Creinin 2007)	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[1]	None	23/554 (4.2%)	16/546 (2.9%)	RR 1.42 (0.76 to 2.65)	12 more per 1000 (from 7 fewer to 48 more)	VERY LOW	IMPORTANT

MID: minimal important difference; RR: relative risk
[1] The confidence interval crosses two MID boundaries
[2] Unblinded RCT
[3] The MID for this outcome is statistical significance, and the imprecision ratings were undertaken on that basis by using the optimum information size so that if the total event rate ≥300, then the quality was not downgraded, if the event rate = 150-299, then the quality was downgraded by 1 level and if the event rate <150, then the quality was downgraded by 2 levels
[4] No MID available for this outcome as it is only reported as medians and ranges. Imprecision ratings were undertaken by 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 1 level and if the total n <200, then the quality was downgraded by 2 levels
[5] Cannot be rated/calculated as the study only reports medians and ranges (hours), not means and standard deviations, which were: Simultaneous: 3.7 (0-74); Delayed: 2 (-23 – 24); p < 0.001 (Mann-Whitney U test)
[6] Cannot be rated/calculated as the study only reports medians and ranges (hours), not means and standard deviations, which were: Simultaneous: 2.5 (0-143); Delayed: 1.7 (-24 – 115); p < 0.001 (Mann-Whitney U test)

Table 4: Comparison 2: Simultaneous oral mifepristone 200 mg and vaginal misoprostol 400 mcg versus vaginal misoprostol 400 mcg 24-48 hours after oral mifepristone 200 mg

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Simultaneous**	**Delayed**	**Relative (95% CI)**	**Absolute**		
Ongoing pregnancy rate												
2 (Goel 2011; Verma 2017)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	0/140 (0%)	1/140 (0.71%)	RR 0.33 (0.01 to 8.09)	5 fewer per 1000 (from 7 fewer to 51 more)	VERY LOW	CRITICAL
Haemorrhage requiring transfusion or 500 ml blood loss or above												
2 (Goel 2011; Verma 2017)	Randomised trials	Very serious[1,3]	No serious inconsistency	No serious indirectness	Very serious[4]	None	0/140 (0%)	0/140 (0%)	Not estimable	Not estimable	VERY LOW	CRITICAL
Patient satisfaction ("Satisfied with procedure and would like to use this method again")												
1 (Goel 2011)	Randomised trials	Very serious[3,5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	39/40 (97.5%)	38/40 (95%)	RR 1.03 (0.94 to 1.12)	28 more per 1000 (from 57 fewer to 114 more)	LOW	CRITICAL
Need for repeat misoprostol												
1 (Goel 2011)	Randomised trials	Very serious[3,5]	No serious inconsistency	No serious indirectness	Very serious[2]	None	2/40 (5%)	1/40 (2.5%)	RR 2 (0.19 to 21.18)	25 more per 1000 (from 20 fewer to 505 more)	VERY LOW	IMPORTANT
Time to onset of bleeding (hours; Better indicated by lower values)												
1 (Goel 2011)	Randomised trials	Very serious[3,5]	No serious inconsistency	No serious indirectness	Serious[6]	None	40	40	Not estimable	MD 0.74 higher (0.07 to 1.41 higher)	VERY LOW	IMPORTANT
Total treatment time from mifepristone to expulsion (Better indicated by lower values)												
1 (Goel 2011)	Randomised trials	Very serious[3,5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	40	40	Not estimable	MD 23.45 lower (24.17 to 22.73 lower)[7]	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Simultaneous**	**Delayed**	**Relative (95% CI)**	**Absolute**		
Incomplete abortion with the need for surgical intervention												
2 (Goel 2011; Verma 2017)	Randomised trials	Very serious[1,3]	No serious inconsistency	No serious indirectness	Very serious[2]	None	6/140 (4.3%)	6/140 (4.3%)	RR 1 (0.33 to 3.03)	0 fewer per 1000 (from 29 fewer to 87 more)	VERY LOW	IMPORTANT

MID: minimal important difference; RR: relative risk; MD: Mean difference

[1] Unclear randomisation sequence generation and/or allocation concealment adequacy in both studies

[2] The confidence interval crosses two MID boundaries

[3] Unblinded RCT

[4] The MID for this outcome is statistical significance, and the imprecision ratings were undertaken on that basis by using the optimum information size so that if the total event rate ≥300, then the quality was not downgraded, if the event rate = 150-299, then the quality was downgraded by 1 level and if the event rate <150, then the quality was downgraded by 2 levels

[5] Unclear adequacy of allocation concealment

*[6] MID 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 confidence interval crossed one MID*

[7] Induction-to-abortion interval (hours) from misoprostol administration is reported. 5.95 (1.81) + 24 hours for delayed group, but SD is not correct then.

Appendix G – Economic evidence study selection

Economic evidence for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

No economic evidence was identified which was applicable to this review question.

Appendix H – Economic evidence tables

Economic evidence tables for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

No economic evidence was identified which was applicable to this review question.

Appendix I –Economic evidence profiles

Economic evidence tables for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

No economic evidence was identified which was applicable to this review question.

Appendix J –Economic analysis

Economic analysis for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

Clinical studies

Study	Reason for Exclusion
Aubeny,E., Chatellier,G., A randomized comparison of mifepristone and self-administered oral or vaginal misoprostol for early abortion, European Journal of Contraception and Reproductive Health Care, 5, 171-176, 2000	Comparison not in PICO
Chen, M. J., Creinin, M. D., Mifepristone With Buccal Misoprostol for Medical Abortion: A Systematic Review, Obstetrics & GynecologyObstet 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), Contraception, 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, New England Journal of Medicine, 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, Acta obstetricia ET gynecologica scandinavica, 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., MacIsaa,L., Amory,J.K., Neuhaus,J., Olkin,I., Creinin,M.D., The efficacy of medical abortion: A meta-analysis, Contraception, 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
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

Study	Reason for Exclusion
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 termination of pregnancy 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
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 and outcomes

Economic studies

No economic evidence was identified for this review. See supplementary material X for further information.

Appendix L – Research recommendations

Research recommendations for review question: For women who are having an early (up to 10^{+0} weeks) medical termination of pregnancy, what is the effectiveness, safety and acceptability of mifepristone and misoprostol given simultaneously compared with other time intervals?

No research recommendations were made for this review question.