Medical termination for pregnancy in early first trimester (≤ 63 days) using combination of mifepristone and misoprostol or misoprostol alone: a systematic review

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Abstract

**Background** A wide range of drugs have been studied for first trimester medical abortion. Studies evaluating different regimens, including combination mifepristone and misoprostol and misoprostol alone regimens, show varying results related to safety, efficacy and other outcomes.

**Objectives** To compare the safety, effectiveness and acceptability of medical abortion and to compare medical methods with surgical methods of abortion ≤ 63 days of gestation.

**Methods** Pubmed and EMBASE were systematically searched from inception through January 2019 using a combination of MeSH, keywords and text words.

Randomized controlled trials on induced abortion at ≤ 63 days that compared different regimens of medical abortion using mifepristone and/or misoprostol and trials that compared medical with surgical methods of abortion were included.

We extracted data into a pre-designed form, calculated effect estimates, and performed meta-analyses where possible. The primary outcomes were ongoing pregnancy and successful abortion.

**Results** Combined regimens using mifepristone and misoprostol had lower rates of ongoing pregnancy and higher rates of successful abortion compared to misoprostol only regimens. In combined regimens, misoprostol 800 \( \mu \text{g} \) appears to be more effective than 400 \( \mu \text{g} \). There was no significant difference with different dosing intervals between mifepristone and misoprostol and routes of misoprostol administration in combination or misoprostol alone regimens. The rate of serious adverse events was generally low.

**Conclusion** In this systematic review, we establish medical methods of abortion utilizing combination mifepristone and misoprostol or misoprostol alone are effective, safe and acceptable. More robust studies evaluating both the different combination and misoprostol alone regimens are needed to strengthen existing evidence as well as assess patient perspectives towards a particular regimen.

**Background**

Medical methods emerged as an alternative to surgical abortion with the discovery of prostaglandins in the early 1970s [1,2,3]. Their use has evolved in the last two decades and various drugs have been used for first trimester medical abortion. Several studies have explored utilization of mifepristone, methotrexate and various prostaglandins with different doses, routes and intervals of administration [4]. A Cochrane review compared different medical methods for first trimester abortion in 2011 and since that time, there has been growing evidence assessing the effectiveness and safety of medical methods using two specific regimens: the combination regimen (mifepristone and misoprostol) and misoprostol alone [5].
The 2012 World Health Organization (WHO) safe abortion guideline had varying regimens for induced abortion at < 12 weeks. With the emergence of new evidence, this systematic review was done as part of the evidence synthesis for the WHO guidance on medical abortion. Options for medical abortion vary globally, and evidence-based guidance is needed to inform clinical care in selecting a regimen. The objectives of this review were to compare the effectiveness, safety and acceptability of different regimens of medical abortion containing mifepristone and/or misoprostol and to compare medical with surgical methods of abortion at ≤ 63 days of gestational age.

**Methods**

**Search strategy**

We searched Pubmed and EMBASE for randomized controlled trials on induced abortion at ≤ 63 days. Our search was from inception through January 2019 using a combination of MeSH, keywords and text words. (Additional file 1)

**Selection criteria**

Inclusion criteria included randomized controlled trials (RCTs) that compared different medication regimens for induced abortion at ≤ 63 days using mifepristone and/or misoprostol; different frequencies of administration of misoprostol in combination regimens; different doses and dosing intervals of misoprostol in combination regimens; different routes of misoprostol in combination regimens; and different dosing regimens and routes in misoprostol only regimens. We also included trials that compared surgical abortion with medical abortion using combination or misoprostol alone regimens. We excluded studies that included induced abortion > 63 days, missed abortion, miscarriage, fetal demise and those that did not report on the primary outcomes. We also excluded studies comparing medical regimens beyond mifepristone and/or misoprostol, such as those using methotrexate or gemeprost. In addition, we excluded studies that compared various mifepristone dosages beyond the WHO recommended 200 mg dose, as a previously conducted Cochrane review showed effectiveness of mifepristone at this lower dose (5).

All search results (titles, abstracts and when necessary, full articles) were screened using the Covidence tool [11].

**Data collection and Analysis**

Data extraction was performed using a standardized data-abstraction form.

The primary outcomes were ongoing pregnancy and successful abortion (defined as uterine evacuation without need for surgical intervention). Secondary outcomes were: safety (defined as serious adverse events and complications; such as hospitalization; blood transfusion; need for further surgery beyond interventions to complete removal of products; or death), expulsion time from initiation of treatment, side effects (including bleeding; pain; and vomiting) and satisfaction.
For dichotomous data (e.g., complete abortion rate), we used the number of events in the control and intervention groups of each study to calculate Risk Ratios (RRs) with 95% confidence intervals for our primary outcome, and secondary outcomes as available. Analyses were conducted using RevMan version 5.3 (Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

We used GRADEpro software and Cochrane methods to evaluate the overall quality of the body of evidence for the main review outcomes. We relied on GRADE criteria (e.g., risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the evidence. The Cochrane Risk of Bias Assessment tool was used to assess risk of bias across studies [12]. We specifically assessed: selection (random sequence generation and allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome assessors); attrition (incomplete outcome data); reporting (selective reporting); and other biases. Studies were ranked as low risk, high risk, or unclear risk using the criteria outlined by the Cochrane Handbook for Systematic Reviews of Interventions [9].

Two review authors (FAA and CK) independently performed study selection, data extraction, assessment of risk of bias and quality of evidence. Discrepancies were resolved by discussion with the third author (MIR).

Results

The initial search yielded 1,506 articles, of which 33 articles fit our inclusion criteria. (Figure 1). Studies included for this review were conducted across 19 countries. Using the World Bank's 2018 classification of economies, the articles represent data from six high income economies, six upper-middle income economies, six lower-middle income economies and one low income economy [13]. The year of publication ranged from 1994 to 2017. The characteristics of the included studies are shown in Table 1. Approximately 85% of the included studies had a low risk of selection bias based on random sequence generation and 78% had a high risk of performance bias (Additional file 2).

Medical regimens

Different regimens of medical abortion management containing combination mifepristone misoprostol, or misoprostol alone were reviewed. Six studies compared combined mifepristone misoprostol vs. misoprostol alone, 6 studies compared different doses of misoprostol in combined regimens, 8 studies compared the timing interval between mifepristone and misoprostol in combined regimens, 13 compared routes of misoprostol in combined regimens, 2 compared various misoprostol alone regimens, and 1 study compared medical with suction evacuation.

1. Combination mifepristone misoprostol compared with misoprostol alone

Three studies compared combined with misoprostol alone regimens [14,15,16] (Table 2).
Women treated with a combined regimen had lower rates of ongoing pregnancy (RR 0.16 CI 95% 0.08-0.31, low certainty of evidence) and higher rates of successful abortion (RR 1.23 CI 95% 1.16-1.30, very low certainty of evidence) compared to women treated with a misoprostol only regimen. The combined regimen resulted in a higher rate of satisfaction (RR 1.13 CI 95% 1.00-1.26, low certainty of evidence) (Table S1, Additional file 3).

2. Comparisons of different regimens of misoprostol when combined with mifepristone

2.1 Comparison of misoprostol doses in combined regimen

Six studies assessed different doses of misoprostol, using the same routes, in combined regimens. These included comparisons of 400 μg buccal vs. 800 μg buccal [6], 400 μg oral twice vs. 400 μg oral once [17], 800 μg oral once vs. 400 μg oral twice [18,19], 400 μg sublingual vs. 800 μg sublingual [7], 400 μg vaginal vs. 800 μg vaginal [7] and 400 μg oral versus 600 μg oral [20] (Table 2).

Women treated with misoprostol 400 μg buccal had lower rates of ongoing pregnancy (RR 0.16 CI 95% 0.08-0.31, moderate certainty of evidence) and higher rates of successful abortion (RR 1.23 CI 95% 1.16-1.30, moderate certainty of evidence) compared to women taking 800 μg buccal [6].

For women taking a total of 800 μg oral misoprostol, there were lower rates of ongoing pregnancy (RR 0.10 CI 95% 0.01-0.80, low certainty of evidence) compared to women taking oral 400 μg [17]. Other studies that investigated 800 μg dosage of misoprostol showed comparable rates of successful abortion between 800 μg oral once and 400 μg oral twice (RR 0.94 CI 95% 0.89-0.99, moderate certainty of evidence) [18,19].

Another significant finding was that women taking 400 μg sublingual misoprostol were more likely to experience ongoing pregnancy compared to the group who took 800 μg misoprostol (RR 3.44 CI 95% 1.14-10.40, moderate certainty of evidence) [7].

Although the remaining comparisons did not provide statistically significant findings, there was moderate certainty on the higher rates of ongoing pregnancy in the 400mcg vaginal misoprostol compared to the 800mcg vaginal misoprostol. (Table 2) Safety and satisfaction appeared to be comparable throughout the groups. (Table S2, Additional file 3).

2.2 Comparison of dosing intervals between mifepristone and misoprostol in combined regimen

Eight studies assessed different time intervals between mifepristone and misoprostol dosing in the combined regimen. These include comparisons between < 8 hours vs. > 24 hours [8,9], 24 hours vs. 48 hours [10,21,22], concurrent administration vs. 24 hours [23,24] and < 8 hours vs. 48 hours [25] (Table 2).

Administration of misoprostol within 8 hours of mifepristone was found to have similar rates of successful abortion compared to 24-hour (RR 0.98 CI 95% 0.91-1.06, moderate certainty of evidence) and 48-hour intervals (RR 0.91 CI 95% 0.66-1.25, very low certainty of evidence) [8,9,25].
There may be little to no difference in rates of successful abortion between concurrent administration of misoprostol and a 24-hour interval (RR 1.01 CI 95% 0.84-1.21, very low certainty of evidence) [23,24]. There was no significant difference between 24-hour and 48-hour interval in terms of ongoing pregnancy and successful abortion [10,21,22]. All dosing interval comparisons showed similar safety and satisfaction rates. (Table S3, Additional file 3).

3. Comparisons of misoprostol routes in combined mifepristone misoprostol regimen

Thirteen studies assessed different routes of misoprostol in the combined regimen (Table 2).

Treatment with 800 $\mu$g oral misoprostol showed higher rates of ongoing pregnancy compared with vaginal (RR 6.70 CI 95% 1.88-23.86, moderate certainty of evidence) and buccal routes (RR 3.61 CI 95% 1.20-10.80, low certainty of evidence) [19,28,29,33].

Women treated with sublingual route were found to have similar rates of successful abortion compared to those treated with vaginal route (RR 0.99 CI 95% 0.92-1.07, moderate certainty of evidence) [7].

There may be little to no difference in successful abortion rates among women treated with buccal route compared to those treated with sublingual (RR 0.98 CI 95% 0.73-1.33, very low certainty of evidence) or vaginal routes (RR 1.00 CI 95% 0.87-1.15, low certainty of evidence) [30, 32].

Safety and satisfaction rates of tested routes appears to be similar. (Table S4, Additional file 3).

4. Comparisons of different misoprostol only regimens

One study compared 7 different misoprostol only regimens [36] (Table 2). In this study, oral misoprostol 400 $\mu$g every 3 hours administered for 4 doses was compared to vaginal misoprostol 600 $\mu$g once and oral misoprostol 800 $\mu$g administered every 6 hours for 2 doses. In another arm, vaginal misoprostol 600 $\mu$g once was compared to oral misoprostol 800 $\mu$g administered every 6 hours for 2 doses.

None of the study arms were shown to be more effective than the other. In addition, we were not able to compare the safety outcomes of these regimens. (Table S5, Additional file 3).

5. Comparisons of medical versus surgical management

One study compared surgical management with medical management using a single dose of 800 $\mu$g vaginal misoprostol [38] (Table 2). Women treated with medical method showed higher rates of ongoing pregnancy (RR 6.70 CI 95% 1.88-23.8). There was little to no difference in rates of successful abortion between the two methods (RR 1.02 CI 95% 0.89-1.17). There was a lower rate of serious adverse events and complications among women who received medical management (RR 0.33 CI 95% 0.01-8.04). The certainty of evidence is very low for all reported outcomes (Table S6, Additional file 3).

Discussion
In this review we identified 33 trials conducted across different settings with a total of 22,275 participants. We compared effectiveness, safety and acceptability of different combination and misoprostol only regimens. Acceptability was not explicitly reported; thus, we used satisfaction, which was reported in 25 of the included studies, as a proxy indicator.

The results of this review demonstrate that the majority of the studies compared different combination and misoprostol alone regimens in terms of dosing, route and frequency of administration. This reflects the fact that mifepristone has replaced older medications, such as methotrexate and gemeprost, when used in combination with misoprostol.

A combined regimen of mifepristone and misoprostol was found to be more effective in terms of lower rates of ongoing pregnancy and higher rates of successful abortion compared to the misoprostol alone regimen [14,15,16].

There have been multiple studies that focus on the combination regimen, comparing various misoprostol doses and routes and the interval between mifepristone and misoprostol.

When comparing different doses of misoprostol in the combined mifepristone misoprostol regimen, the included studies focused on the dosages of 400 µg and 800 µg. Comparing 400 µg to 800 µg buccal misoprostol [6], treatment with 400 µg misoprostol was found to be more effective (moderate certainty of evidence). On the other hand, administration of 800 µg oral misoprostol demonstrated more effectiveness than 400 µg oral misoprostol. Moreover, there is moderate certainty of evidence that 800 µg sublingual misoprostol is 3 times more effective than 400 µg [7]. Although there were multiple comparisons, it appears that the dosage of 800 µg of misoprostol in the combined mifepristone misoprostol regimen showed higher effectiveness with lower rates of ongoing pregnancy and higher rates of successful abortion. In addition, 800 µg were associated with higher rates of satisfaction [6,7].

Review of studies that compared different dosing interval between mifepristone and misoprostol in combined regimen showed inconclusive results. Individual studies showed a 24-hour interval to be more effective compared to either 8- or 48-hour intervals [5-7,21,22]. However, we were not able to replicate these findings in the pooled analysis. We found similar rates of effectiveness between 24-hour and 48-hour intervals. In addition, the safety profile and satisfaction rates were not significantly different.

Comparing 8-hour interval to 24-hour and 48-hour intervals showed that a shorter interval of misoprostol administration did not compromise effectiveness significantly [8,9]. Furthermore, a 24-hour interval was no more effective than concurrent administration. Our results align with existing evidence that demonstrates that concurrent administration can lead to higher satisfaction rates [5,23,24], while also impacting the number of visits required and time needed to complete the procedure [5]. Nonetheless, satisfaction rate was not consistently reported across studies. Thus, further study is needed to assess the impact of dosing interval on this outcome and how it relates to the acceptability of the procedure to women.
When comparing studies to determine optimal routes of misoprostol in combined mifepristone misoprostol regimen, there were mixed results. There is moderate certainty of evidence that oral misoprostol is significantly less effective than vaginal misoprostol [19,28,29]. Similarly, oral route was found to be less effective than buccal route (low certainty of evidence) [33]. However, individual studies show oral administration of misoprostol in the combined regimen was found to have better overall satisfaction [19,28-30].

Buccal route was found to be as effective as sublingual and vaginal route and there was no significant difference between sublingual and vaginal routes [30,31,32]. Given the findings of the non-significant differences between the routes, woman should be given the full range options factoring in their satisfaction towards a particular treatment regimen. This is particularly important as satisfaction towards a particular regimen was not assessed in all studies.

A review of one study with 7 different arms comparing misoprostol only regimens failed to demonstrate superiority of one regimen over the others. This potentially means that the suggested misoprostol doses are just as good as the other but at this time no conclusions can be made without additional studies evaluating the misoprostol only regimens. This would be important to address the needs of those who cannot afford or access mifepristone [36].

Compared to surgical method, medical management was found to have significantly higher rates of ongoing pregnancy. Lower rates of serious adverse events and complications were observed with medical methods [38]. However, interpretation of this finding requires caution as it was based on only one trial and certainty of evidence was very low.

One study comparing oral versus vaginal misoprostol reported one woman in the vaginal arm who died from a systemic *Clostridium sordellii* infection [20]. However, in general, the rates of serious adverse events reported in our review are very low, thus we cannot draw definitive conclusions related to adverse events.

**Strengths and limitations**

This review has several strengths. We used a comprehensive and replicable search strategy to identify relevant articles. In addition, the included studies were conducted across different settings. We employed the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) system that can assist health care providers, program managers and policy makers to design and implement best practice recommendation and guidelines.

Limitations of this review include the inclusion of only RCTs and using satisfaction as a proxy for acceptability. Specifically, inclusion of observational studies could be more informative about client satisfaction and acceptability of treatment regimens. We were not able to demonstrate statistically significant differences for various dosing intervals and routes of misoprostol administration in combination or in misoprostol alone regimens. For some of the comparison arms (medical vs. surgical,
misoprostol only regimens), there are a limited number of studies. In addition, some of the included studies have a high risk of performance bias and detection bias. Thus, we recommend future research studies to consider blinding of outcome assessor as it is feasible to blind the individual who is assessing the success of the abortion (whether by history, physical exam or ultrasound) and this in turn can improve the quality of data.

**Conclusion**

In this systematic review, we establish that medical methods of abortion are effective, safe and acceptable for termination of pregnancy for \( \leq 63 \) days of gestation. The combined regimen of mifepristone and misoprostol was found to be more effective than the misoprostol alone regimen. In the combined regimen, the dosage of 800 \( \mu g \) misoprostol appears to be more effective than 400 \( \mu g \). Although there were no significant differences found with the dosing interval and the routes of misoprostol, the additive information on the certainty of evidence and consideration of women's satisfaction, suggest that a 24-hour interval and offering different routes of administration are an effective, safe and acceptable options for medical abortion. This further highlights the fact that in many cases, demonstrating that one option versus another is not statistically significant allows the clinical decision to then be made as to the individual's preference. More robust studies evaluating both the different combination and misoprostol alone regimens are needed to strengthen existing evidence as well as assess patient perspectives towards a particular regimen.

**List Of Abbreviations**

CI: Confidence Interval

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

RCTs: Randomized Controlled Trials

RR: Risk Ratio

WHO: World Health Organization

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable
**Availability of data and materials**

The datasets supporting the conclusions of this article are included within the article and its additional files.

**Competing interests**

The authors declare that they have no competing interests.

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**Author contributions**

The initial review was conducted as part of the evidence synthesis for the WHO guidance on medical abortion. AL had overall responsibility of the guideline development and coordinated the work. FAA and CK conceived the idea and conducted the search, screening, data extraction and quality assessments. MIR carried out the analysis and assessed the overall quality and validity of the evidence with the GRADE (grading of recommendations assessment, development and evaluation) system. FAA and CK wrote the first draft of the manuscript. All authors participated in the revision and writing of the final manuscript.

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**Tables**

Due to technical limitations the tables are available as a download in the Supplementary Files

**Figures**
Figure 1

PRISMA flow diagram

Supplementary Files

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