Medical termination for pregnancy in early first trimester (≤ 63 days): 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 regimen.

Conclusion In this systematic review, we establish medical methods of abortion utilizing combination mifepristone/misoprostol or misoprostol alone are effective, safe and acceptable. In combined regimen, misoprostol 800 μg given vaginally or sublingually had lower rates of ongoing pregnancy and higher rates of successful abortion with moderate certainty of evidence.

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 the different medical methods for first trimester abortion in 2011 and since that time, there has been growing evidence assessing effectiveness and safety of the medical methods, in particular with the combination regimen (mifepristone and misoprostol) and misoprostol alone [5].

However, individual studies evaluating medical management of abortion at ≤63 days have not demonstrated superiority of one regimen. Specifically, studies have looked at different routes and doses of misoprostol in combined regimens [6,7], as well comparing different intervals between mifepristone and misoprostol [8–10].

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. Thus, the objectives of this review were to compare the effectiveness, safety and acceptability of different regimens of medical abortion
containing mifepristone and misoprostol and to compare medical with surgical methods of abortion at \( \leq 63 \) days of gestational age.

**Methods**

**Search strategy**

We searched Pubmed and EMBASE for randomized controlled trials on induced abortion at \( \leq 63 \) 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 \( \leq 63 \) 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, gemeprost, as well as studies that compared various mifepristone dosages beyond the WHO recommended 200mg dose.

All search results (titles, abstracts and when necessary, full articles) were screened independently by two authors (FAA and CK) using the Covidence tool [11]. Any discrepancies between the reviewers were reviewed by a third author (MIR) and resolved by consensus.

**Data collection and Analysis**

Data extraction was performed using a standardized data-abstraction form. Two authors (FAA and CK) independently performed the data extraction and assessed risk of bias. Disagreements were resolved by discussion with the third author (MIR).

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 Review of Intervention [9]. Two review authors (FAA and CK) worked independently to judge the evidence quality (e.g., high, moderate, low, or very low) and risk of bias. Any disagreements were arbitrated by a third author (MIR) and resolved by discussion.

**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** [14,15,16]
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 include comparison of 400 $\mu$g buccal vs. 800 $\mu$g buccal [6], 400 $\mu$g oral twice vs. 400 $\mu$g oral once [17], 800 $\mu$g oral single dose vs. 400 $\mu$g oral twice [18,19], 400 $\mu$g sublingual vs. 800 $\mu$g sublingual [7], 400 $\mu$g vaginal vs. 800 $\mu$g vaginal [7] and 400 $\mu$g oral versus 600 $\mu$g oral [20].

a. **Misoprostol buccal 400 $\mu$g versus 800 $\mu$g [6]**

Women treated with 400 $\mu$g misoprostol had lower rates of ongoing pregnancy (RR 0.16 CI 95% 0.08-0.31) and higher rates of successful abortion (RR 1.23 CI 95% 1.16-1.30). The certainty of evidence for both outcomes is moderate. More women in the 800 $\mu$g group reported satisfaction towards their regimen, very low certainty of evidence (Table S2A, Additional file 3).

b. **Misoprostol oral 400 $\mu$g twice (800 total) versus 400 $\mu$g once [17]**

Women treated with misoprostol 400 $\mu$g oral twice had lower rates of ongoing pregnancy (RR 0.10 CI 95% 0.01-0.80) and higher rates of successful abortion (RR 1.03 CI 95% 0.86-1.23). More women who took misoprostol twice reported satisfaction towards their regimen. The certainty of evidence is low for reported outcomes. (Table S2B, Additional file 3).

c. **Misoprostol oral 400 $\mu$g twice versus 800 $\mu$g single dose [18,19]**

More women treated with 400 $\mu$g misoprostol twice experienced ongoing pregnancy. (RR 0.88 CI 95% 0.24-3.19). Women treated with single dose of 800 $\mu$g misoprostol had lower rates of successful abortion (RR 0.94 CI 95% 0.89-0.99). The certainty of evidence for both outcomes is moderate. (Table S2C, Additional file 3).

d. **Misoprostol sublingual 400 $\mu$g versus 800 $\mu$g [7]**

Women treated with 400 $\mu$g sublingual misoprostol had higher rates of ongoing pregnancy (RR 3.44 CI 95% 1.14-10.40) and lower rates of successful abortion (RR 0.99 CI 95% 0.92-1.07). The certainty of evidence for both outcomes is moderate. More women were satisfied in the 800 $\mu$g group, low certainty of evidence. (Table S2D, Additional file 3).
e. Misoprostol vaginal 400 μg versus 800 μg [7]

Women treated with 400 μg vaginal misoprostol had higher rates of ongoing pregnancy (RR 2.23 CI 95% 0.98-5.11) and lower rates of successful abortion (RR 0.97 CI 95% 0.90-1.05). The certainty of evidence for both outcomes is moderate. More women in the 800 μg reported satisfaction towards their regimen, low certainty of evidence. (Table S2E, Additional file 3).

f. Misoprostol oral 400 μg versus 600 μg [20]

Women treated with 400 μg oral misoprostol had lower rates of ongoing pregnancy (RR 0.33 CI 95% 0.01-8.10) and higher rates of successful abortion (RR 1.01 CI 95% 0.91-1.13). More women treated with 400 μg oral misoprostol were satisfied with their regimen. The certainty of evidence is low for the reported outcomes. (Table S2F, 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].

a. Misoprostol 800 μg vaginal given < 8 hours versus > 24 hours after mifepristone [8,9]

Women who took misoprostol < 8 hours after mifepristone had higher rates of ongoing pregnancy (RR 2.23 CI 95% 0.69-7.2) and lower rates of successful abortion (RR 0.98 CI 95% 0.91-1.06). The certainty of evidence is moderate for both outcomes. (Table S3A), Additional file 3.

b. Misoprostol 400-800 μg vaginal given 24 hours versus 48 hours after mifepristone [10,21,22]

Women treated with misoprostol 24 hours after mifepristone had lower rates of ongoing pregnancy (RR 0.92 CI 95% 0.40-2.12). This regimen had lower rates of successful abortion (RR 0.99 CI 95% 0.80-1.23) compared to misoprostol administration 48 hours after mifepristone. The certainty of evidence is very low for both outcomes (Table S3B, Additional file 3).

c. Misoprostol 400 μg vaginal given concurrently versus 24 hours after mifepristone [23,24]

Among women treated with concurrent administration, there were higher rates of successful abortion (RR 1.01 CI 95% 0.84-1.21). There was no difference in the rate of ongoing pregnancy. More women reported satisfaction with concurrent administration. The certainty of evidence is very low the reported outcomes (Table S3C, Additional file 3).

d. Misoprostol 400 μg oral given < 8 hours versus 48 hours after mifepristone [25]
Women treated with misoprostol < 8 hours after mifepristone had lower rates of successful abortion (RR 0.91 CI 95% 0.66-1.25). There was no difference in the rate of ongoing pregnancy between the two groups. The certainty of evidence is very low for the reported outcomes. (Table S3D, Additional file 3).

3. **Comparisons of misoprostol routes in combined mifepristone-misoprostol regimen**

Thirteen studies assessed different routes of misoprostol in combined regimen (Table S6).

**a. Misoprostol vaginal versus sublingual** [7,26,27]

In a study comparing 400 µg vaginal misoprostol versus sublingual route, treatment with the sublingual route showed lower rates of ongoing pregnancy (RR 0.79 CI 95% 0.39-1.55) and higher rates of successful abortion (RR 1.01 CI 95% 0.94-1.09). The certainty of evidence is moderate for the reported outcomes [7] (Table S4A, Additional file 3).

The same study also compared 800 µg misoprostol administered vaginally versus sublingually using combined regimens. More women in the sublingual arm experienced ongoing pregnancy (RR 0.50 CI 95% 0.15-1.67). Treatment with the vaginal route showed lower rates of successful abortion (RR 0.99 CI 95% 0.92-1.07). The certainty of evidence is moderate for both outcomes. More women in the sublingual arm reported satisfaction towards their regimen [7]. (Table S4B, Additional file 3).

Two trials compared administration of 800 µg vaginal misoprostol versus either 600 or 800 µg sublingual misoprostol [26,27]. Those treated with the sublingual route showed lower rates of ongoing pregnancy (RR 0.15 CI 95% 0.08-3.05) and higher rates of successful abortion (RR 1.01 CI 95% 0.87-1.18). The certainty of evidence is low for both reported outcomes (Table S4C, Additional file 3).

**b. Misoprostol oral versus vaginal** [19,20,28,29]

Three trials compared 800 µg misoprostol administered orally compared to vaginally using combined regimens [19,28,29]. Treatment with the oral route had higher rates of ongoing pregnancy (RR 6.70 CI 95% 1.88-23.86) and a lower rate of successful abortion (RR 0.94 CI 95% 0.85-1.04). The certainty of evidence is moderate for both reported outcomes (Table S4D, Additional file 3).

In two studies comparing 400 µg oral misoprostol versus 800 µg vaginal misoprostol in the combined regimen, more women in the oral misoprostol group experienced ongoing pregnancy (RR 2.38 CI 95% 0.34-16.81). Treatment with the oral route had lower rates of successful abortion (RR 0.98 CI 95% 0.91-1.04). The certainty of evidence is moderate for both reported outcomes. More women in the oral arm reported satisfaction towards their regimen [19,20] (Table S4E, Additional file 3).

**c. Misoprostol buccal versus sublingual** [30,31]
One trial compared 800 μg misoprostol administered buccally versus sublingually in combined regimens [30]. Treatment with the buccal route had lower rates of successful abortion (RR 0.98 CI 95% 0.73-1.33). There was no difference in the rate of ongoing pregnancy between the two groups. The certainty of evidence is very low for both reported outcomes (Table S4F, Additional file 3).

In another study comparing 400 μg misoprostol via buccal versus sublingual route in the combined regimen, women treated with buccal misoprostol had higher rates of ongoing pregnancy (RR 1.55 CI 95% 0.22-11.03) and lower rates of successful abortion (RR 0.98 CI 95% 0.91-1.04). More women in the buccal arm reported satisfaction with their regimen. The certainty of evidence is low for the reported outcomes [31] (Table S4G, Additional file 3).

d. Misoprostol buccal versus vaginal [32]

One study compared 800 μg misoprostol administered buccally versus vaginally using combined regimens. Fewer women in the buccal misoprostol arm experienced ongoing pregnancy (RR 0.49 CI 95% 0.09-2.68). There was no difference in the rates of successful abortion between the two groups. Fewer women in the buccal misoprostol reported satisfaction towards their regimen. The certainty of evidence is low for the reported outcomes (Table S4H, Additional file 3).

e. Misoprostol oral versus buccal [33]

One study compared 800 μg misoprostol administered orally versus buccally in combined regimens. Treatment with the oral route showed higher rates of ongoing pregnancy (RR 3.61 CI 95% 1.20-10.80) and lower rates of successful abortion (RR 0.97 CI 95% 0.88-1.07). More women in the oral group reported satisfaction towards their regimen. The certainty of evidence is low for the reported outcomes (Table S4I, Additional file 3).

f. Misoprostol oral versus sublingual [34,35]

Two trials compared 400 μg misoprostol oral versus sublingual routes in combined regimens. Women treated with the oral route had lower rates of ongoing pregnancy (RR 0.44 CI 95% 0.10-1.96) and higher rates of successful abortion (RR 1.03 CI 95% 0.99-1.07). More women in the oral misoprostol group reported satisfaction towards their regimen. The certainty of evidence is low for the reported outcomes (Table S4J, Additional file 3).

4. **Comparisons of different misoprostol only regimens** [36,37]

One study compared 7 different misoprostol only regimens for induced abortion up to 63 days of gestation. One arm compared oral misoprostol 400 μg every 3 hours administered for 4 doses to vaginal misoprostol 600 μg once. Women treated with 400 μg oral misoprostol had higher rates of ongoing pregnancy (RR 1.50 CI 95% 0.67-3.30) and lower rates of successful abortion (RR 0.94 CI 95% 0.52-1.70).
In addition, women taking this regimen had lower rates of satisfaction compared to those who took vaginal misoprostol 600 μg once. The certainty of evidence is very low for the reported outcomes. (Table S5A, Additional file 3).

In another arm, oral misoprostol 800 μg administered every 6 hours for 2 doses was compared with vaginal misoprostol 600 μg once; treatment with the former regimen resulted in lower rates of ongoing pregnancy (RR 0.86 CI 95% 0.28-2.59), higher rates of successful abortion (RR 1.12 CI 95% 0.61-2.05). Women taking this regimen also reported higher rates of satisfaction. The certainty of evidence is very low for the reported outcomes (Table S5B, Additional file 3).

The same study also compared oral misoprostol 400 μg every 3 hours for 4 doses to oral misoprostol 800 μg every 6 hours twice. Women treated with oral misoprostol 400 μg had higher rates of ongoing pregnancy (RR 1.75 CI 95% 0.62-4.90) and lower rates of successful abortion (RR 0.84 CI 95% 0.44-1.59). In addition, more women using 800 μg found the regimen acceptable compared to women treated with oral misoprostol 400 μg. The certainty of evidence is very low for the reported outcomes (Table S5C, Additional file 3).

Comparisons of medical versus surgical management[38]

One study compared surgical management with medical management using a single dose of 800 μg vaginal misoprostol. There was no difference in the rates of ongoing pregnancy. More women who were managed with misoprostol had successful abortion compared to women who were managed with the surgical method (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. The results indicate that medical methods are effective, safe and acceptable for termination of pregnancy for ≤63 days of gestation. We used satisfaction, which was reported in 25 of the included studies, as a proxy indicator of acceptability.

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.

There have been multiple studies that focus on the combination regimen, comparing various misoprostol doses and routes and the interval between mifepristone and misoprostol. From the studies that compared different doses of misoprostol in combined mifepristone/misoprostol regimen, the use of 800 μg of misoprostol in the combined regimen had lower rates of ongoing pregnancy and higher rates of
successful abortion based on moderate certainty of evidence. Regimens including 800 μg were also associated with higher satisfaction rates. In one study that compared 400 μg versus 800 μg buccal misoprostol [6], treatment with 400 μg misoprostol showed lower rates of ongoing pregnancy and higher rates of successful abortion. However, a higher satisfaction rate was noted in the 800 μg arm. In addition, women treated with single dose 800 μg misoprostol group had lower rates of bleeding and pain compared to those treated with 400 μg administered twice 2 hours apart [18,19].

Of the studies that compared the interval timing between mifepristone and misoprostol, a 24-hour interval resulted in greater efficacy. Moreover, compared to concurrent administration and a 48 hour interval, the 24 hour interval showed lower rates of side effects of bleeding, pain and vomiting [10,21–23].

Comparisons of the routes of misoprostol administration revealed that utilization of either vaginal or sublingual routes of misoprostol in the combined regimen achieves lower rates of ongoing pregnancy and higher successful abortion. One study comparing vaginal and sublingual route reported higher satisfaction rates with the sublingual route [7]. Compared to vaginal and buccal routes, oral administration of misoprostol in the combined regimen was found to have a lower rate of serious adverse events and better overall satisfaction [19,28–30].

A review of one study with 7 different arms comparing misoprostol only regimens demonstrated that oral misoprostol 800 μg administered every 6 hours for 2 doses resulted in lower rates of ongoing pregnancy, higher rates of successful abortion and higher rates of satisfaction [36].

In one study that compared medical to surgical management, medical management was found to have higher rates of successful abortion and there was no difference in the rates of ongoing pregnancy. In addition, there was a lower rate of serious adverse events and complications with medical methods [38].

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 rate of serious adverse events reported in our review are very low, thus we cannot draw definitive conclusions related to adverse events.

The results of this review demonstrate that the majority of the studies assessed outcomes of 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.

Studies that assessed the outcomes of different intervals between mifepristone and misoprostol administration in combined regimens showed a 24 hour interval to be more effective compared to either 8 or 48 hour intervals [5–7,21,22]. However, concurrent administration was found to have no difference in the rate of ongoing pregnancy and a higher satisfaction rate when compared to a 24 hour interval [23,24]. This can have significant impact on the time needed to complete the procedure, the number of visits and satisfaction rate. However, 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.

Though vaginal and sublingual routes of misoprostol in combined regimen were more effective in terms of ongoing pregnancy and success, oral administration was found to have lower rates of serious adverse events and higher satisfaction compared to vaginal route. Thus, woman should be given the full range options factoring in their satisfaction towards a particular treatment regimen.

**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. Furthermore, for some of the comparisons arms (medical vs. surgical, misoprostol only regimens), there are a limited number of studies. Furthermore, some of the included studies have a high risk of performance bias and detection bias. Thus, we recommend future researches 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. Specifically, a combined regimen of mifepristone and misoprostol containing 800 μg of misoprostol given 24 hours after mifepristone either vaginally or sublingually was found to be an effective, safe and acceptable method for termination of pregnancy ≤63 days of gestation.

**List Of Abbreviations**

CI: Confidence Interval

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

RCTs: Randomized Controlled Trials

RR: Risk Ratio
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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Table

**Table 1- Characteristics of included studies**
| S.No | Author, year | Methods | Setting | Participants | Interventions |
|------|--------------|---------|---------|--------------|---------------|
| 1.   | Blanchard et al 2005 | Randomized controlled trial | KEM Hospital in Pune, India, and Hungvuong Hospital in Ho Chi Minh City, Vietnam. | Women seeking pregnancy termination at 56 days or less of amenorrhea. All eligible women had a transvaginal ultrasound scan to confirm duration of pregnancy. | Misoprostol oral 400 μg every 3 hours for 4 doses (N=36) vs. Misoprostol oral 800 μg every 6 hours for 2 doses (N=24) vs. Misoprostol vaginal 600 μg for 1 dose (N=40) |
| 2.   | Blum et al 2012 | Randomized controlled trial | Two large maternity hospitals: the Centre de Maternite et Neonatologie de la Rabta in Tunisia (n=193) and Hung Vuong Hospital, Ho Chi Minh City, Vietnam (n=248). | Pregnant women presenting for early medical abortion up to 63 days since their last menstrual period. | Mifepristone + misoprostol combined Mifepristone 200 mg on day 1 and 800 μg buccal misoprostol followed by placebo 3 hours later on day 2 (N=220) vs. Misoprostol alone Placebo on day 1 and 1600 μg of misoprostol (2 doses of 800 μg, given 3 hours apart) on day 2 (N=221) |
| 3.   | Chai et al 2013 | Randomized controlled trial | Conducted at the Family Planning Association in Hong Kong. | Healthy women aged 18 years or older who requested termination of pregnancy of up to 63 days’ gestation. A transvaginal ultrasound examination was performed to verify the duration of pregnancy and to | Misoprostol buccal Misoprostol buccal 800 μg (four 200 μg misoprostol buccal and four sublingual placebo) 48 hours after receiving |
| Study Number | Authors | Study Design | Location | Intervention 1 | Intervention 2 |
|--------------|---------|--------------|----------|----------------|----------------|
| 4.           | Chawdhry et al 2009 | Randomized controlled trial | Department of Obstetrics and Gynecology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal. | Trans vaginal ultrasound demonstrating an intact single intrauterine pregnancy up to a 63-day period of gestation. | Mifepristone + misoprostol combined Mifepristone 200 mg on day 1 and vaginal misoprostol 800 μg on day 3 (N=50) vs. Misoprostol alone Misoprostol vaginal (800 μg) on day 1 and 3 (total dose 1600 μg) (N=50) |
| 5.           | Chong et al 2012 | Randomized controlled trial | Three clinics in the Republic of Georgia and at Hoc Mon Hospital in Vietnam. | Women who presented for termination of pregnancy with gestations up to 63 days since LMP. | Misoprostol buccal 400 μg Misoprostol buccal 400 μg (two 200 μg misoprostol and two placebo pills) 36-48 hours after mifepristone (N=559) vs. Misoprostol buccal 800 μg Misoprostol buccal 800 μg (four 200 μg mifepristone (N=45) vs. Misoprostol sublingual Misoprostol sublingual 800 μg (four 200 μg misoprostol sublingual and four buccal placebo) 48 hours after receiving mifepristone (N=45) |
| No. | Authors | Study Design/Setting | Participants | Intervention | Outcome |
|-----|---------|----------------------|--------------|--------------|---------|
| 6.  | Coyaji et al 2007 | Randomized controlled trial | K.E.M. Hospital in Pune (n = 150) and the Health Centre, Larsen and Toubro Limited, Mumbai, India (n = 150). | Women seeking termination of pregnancies could participate if they had amenorrhoea of 8 weeks or less. | Two doses of misoprostol pills) 36-48 hours after mifepristone (N=563) |
|     |         |                      |              |              |         |
| 7.  | Creinin et al 2007 | Randomized controlled trial | Four centers: The University of Pittsburgh, Oregon Health and Science University, Northwestern University, and the University of Southern California. The University of Pittsburgh served as the sponsoring institution. | Healthy women requesting an elective abortion, had an intrauterine pregnancy less than or equal to 63 days of gestation on the day of mifepristone administration as confirmed by vaginal ultrasound. | Misoprostol 800 μg vaginal immediately after taking mifepristone (N=567) vs. Misoprostol 800 μg vaginal misoprostol 24 hours after taking mifepristone (N=561) |
| 8.  | Dahiya et al 2011 | Randomized controlled trial | Postpartum center at PGIMS Rohtak, India. | Healthy women with intrauterine pregnancy <56 days based on menstrual history and clinical examination. | Misoprostol oral 400 μg 24 h after mifepristone (N=48) vs. Misoprostol sublingual 400 μg 24 h after |
|   | Study | Design | Location | Eligibility Criteria | Intervention                        | Outcome |
|---|-------|--------|----------|----------------------|--------------------------------------|---------|
| 9. | Dahiya et al 2012 | Randomized controlled trial | Outpatient department of Obstetrics and Gynecology of Pt BDSharma PGIMS, Rohtak, India. | Women with amenorrhea <56 days, age >18 years, request for elective abortion with the indication as per the guidelines of the 1971 MTP act. | Mifepristone + misoprostol combined (N=45) | |
| 10. | El-Refaey et al 1994 | Randomized controlled trial | Department of Obstetrics and Gynaecology, University of Aberdeen | Women requesting termination of pregnancy of less than 56 days amenorrhea confirmed by ultrasound scan examination and fulfilling the criteria of the 1967 Abortion Act. | Misoprostol oral 800 μg single dose 36-48 hours after mifepristone (N=75) vs. Misoprostol vaginal 800 μg 36-48 hours after mifepristone (N=133) |
| 11. | El-Refaey et al 1995 | Randomized controlled trial | Fertility-control clinic, Aberdeen Royal Hospitals, Aberdeen, Scotland. | Women requesting termination of pregnancy within 63 days from the onset of amenorrhea and fulfilling the criteria of the 1967 Abortion Act. | Misoprostol oral 800 μg 36-48 hours after mifepristone (N=130) vs. Misoprostol vaginal 800 μg 36-48 hours after mifepristone (N=133) |
| 12. | Fekih et al 2010 | Randomized controlled trial | Department of Obstetrics and Gynecology in Farhat Hached Teaching Hospital, Sousse, Tunisia. | Women requesting 1st trimester abortion of less than or equal to 56 days from their last menstrual period, determined by vaginal probe | Mifepristone + misoprostol combined (N=50) |
| Study | Title | Design | Setting | Participants | Intervention | Results |
|-------|-------|--------|---------|--------------|-------------|---------|
| 13. Goel et al 2011 | Randomized controlled trial | Obstetrics and Gynaecology Department, MMIMSR, Mullana (Ambala), Haryana, India. | Healthy pregnant women, who were requesting an elective abortion and had a single intrauterine pregnancy of <7 weeks (49 days) of gestation as confirmed by transvaginal ultrasonography. | Misoprostol vaginal 400 μg simultaneously with mifepristone (N=40) | Misoprostol alone Misoprostol sublingual 800 μg (repeated every 4 hours for up to a maximum of 3 doses) (N=126) |
| 14. Guest et al 2007 | Randomized controlled trial | Ninewells Hospital, Dundee, Scotland. | An IUP confirmed on pelvic ultrasound scan, gestation not exceeding 63 days at the administration of mifepristone and participants must be aged 16 years or older, seeking a termination of pregnancy. | Misoprostol vaginal 800 μg after 6 hours of mifepristone (N=225) | |
| 15. Hamoda et al 2005 | Randomized controlled trial | Aberdeen Royal Infirmary, United Kingdom. | Women with a viable singleton IUP (confirmed by transvaginal ultrasound scan) requesting medical abortion up to 13 weeks of gestation. Data aggregated by gestational age. | Misoprostol sublingual 600 μg followed 3 hours later by a further dose of 400 μg sublingual misoprostol (N=57) | |
| No. | Authors | Study Type | Participants | Intervention | Comparator |
|-----|---------|------------|--------------|--------------|------------|
| 16. | Jain et al 2002 | Randomized controlled trial | Women's and Children's Hospital and affiliated clinics, Los Angeles County-University of Southern California Medical Center and San Francisco General Hospital, University of California, San Francisco, United States. | A total of 250 healthy women desiring termination of pregnancies < 56 days gestation were enrolled. | Mifepristone + misoprostol combined Mifepristone 200 mg followed after 48 hours by 800 μg of vaginal misoprostol (repeated every 24 hours for up to a maximum of 3 doses) (N=125) vs. Misoprostol alone Placebo on day 1 and misoprostol vaginal 800 μg repeated every 24 hours for up to a maximum of 3 doses (N=125) |
| 17. | Middleton et al 2005 | Randomized controlled trial | Two sites in Rochester, NY, United States. | Women seeking abortion with pregnancies through 56 days LMP. | Misoprostol buccal 800 μg 1-2 days after mifepristone (N=223) vs. Misoprostol vaginal 800 μg 1-2 days after mifepristone (N=219) |
| 18. | Ngoc et al 2011 | Randomized controlled trial | Tertiary hospital in Ho Chi Minh City, Vietnam. | Women with GA up to 63 days by LMP, living and working within an hour from the hospital desiring medical abortion. | Mifepristone + misoprostol combined Mifepristone 200 mg followed 24 hour later by 800 μg buccal misoprostol |
| Study ID | Authors | Trial Design | Location | Inclusion Criteria | Intervention Details |
|----------|---------|--------------|----------|--------------------|----------------------|
| 19.      | Prasad et al 2009 | Randomized controlled trial | Department of Obstetrics and Gynecology, Maulana Azad Medical College, New Delhi, India. | Women with GA up to 49 days confirmed by clinical examination and pelvic ultrasound seeking abortion. | Medical abortion—misoprostol vaginal 800 μg (N=70) vs. Surgical intervention (N=70) |
| 20.      | Raghavan et al 2009 | Randomized controlled trial | University Clinic, Municipal Clinical Hospital No.1, Chisinau, the Republic of Moldova. | The date of onset of last menses plus pelvic examination were used to calculate gestational age, with ultrasound confirmation as needed. | Misoprostol sublingual 400 μg 24 hours after mifepristone (N=240) vs. Misoprostol oral 400 μg 24 hours after mifepristone (N=240) |
| 21.      | Raghavan et al 2010 | Randomized controlled trial | University Clinic, Municipal Clinical Hospital No.1, Chisinau, the Republic of Moldova. | Women with gestational age through 63 days by LMP presenting for abortion. Gestational age was determined by one or more assessment method: last menses method, pelvic examination and ultrasound. | Misoprostol buccal 400 μg 24 hours after mifepristone (N=277) vs. Misoprostol sublingual 400 μg 24 hours after mifepristone (N=273) |
| #  | Authors          | Study Design          | Setting                                                                 | Inclusion Criteria                                                                 | Interventions                                                                 |
|----|------------------|-----------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| 22 | Schaff et al 2000 | Randomized controlled trial | Sixteen US primary care and referral abortion facilities.                | Participants were at least 18 years old, no more than 56 days pregnant, healthy and desired an abortion. |
| 23 | Schaff et al 2001 | Randomized controlled trial | Multicenter study at 15 sites in United States.                          | Women no more than 63 days pregnant, confirmed by sonogram, desiring an abortion.    | Misoprostol oral 800 μg 24 hours after mifepristone and 400 μg, then another 400 μg misoprostol 2 hours later, last dose no later than midnight on day 2 (N=548) vs. Misoprostol vaginal 800 μg 24 hours after mifepristone (N=596) |
| 24 | Schaff et al 2002 | Randomized controlled trial | Multicenter study at 14 sites in United States                          | Women no more than 63 days pregnant, confirmed by sonogram, desiring an abortion.    | 1) Misoprostol oral 400 μg 48 hours after mifepristone (N=220) vs. 2) Misoprostol oral 800 μg 48 hours after mifepristone (N=269) vs. 3) Misoprostol vaginal 800 μg 48 hours after |
| 25. | Shannon et al 2006 | Randomized controlled trial | Three clinics associated with major research universities in Canada; two in major urban areas and one in a periurban area. | Women aged 16 years or older, seeking elective abortion of pregnancies less than 56 days since last menstrual period or on vaginal ultrasound. | 1) Misoprostol oral 400 μg 24-48 hours after mifepristone (N=319) vs. 2) Misoprostol oral 600 μg 24-48 hours after mifepristone (N=319) vs. 3) Misoprostol vaginal 800 μg 24-48 hours after mifepristone (N=318) |
| 26. | Tang et al 2003 | Randomized controlled trial | Department of Obstetrics and Gynaecology, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China. | Women with gestational age of less than 9 weeks, confirmed by US, requesting legal termination of pregnancy. | Misoprostol sublingual. Misoprostol sublingual 800 μg (and four tablets of vaginal placebo) 48 hours after receiving mifepristone (N=112) vs. Misoprostol vaginal. Misoprostol vaginal 800 μg (and four tablets of sublingual placebo) 48 hours after receiving mifepristone (N=112) |
| 27. | Tendler et al 2015 | Randomized controlled trial | Department of Obstetrics and Gynecology, Galilee Medical Center, Nahariya, Israel. | Women no more than 55 days gestational age desiring medical abortion. | Misoprostol oral 400 μg 2 hours after mifepristone (N=50) vs. |
| 28. | Verma et al 2011 | Randomized controlled trial | Department of Obstetrics and Gynaecology, Hind Institute of Medical Sciences, India. | Women less than 63 days of gestation choosing medical abortion. | Misoprostol oral 400 μg 48 hours after mifepristone (N=50) |
| 29. | Verma et al 2017 | Randomized controlled trial | Department of Obstetrics and Gynaecology, Hind Institute of Medical Sciences, India. | Women up to 63 days of gestation choosing medical abortion. | Misoprostol vaginal 400 μg 24 hours after mifepristone (N=100) vs. Misoprostol vaginal 400 μg 48 hours after mifepristone (N=100) |
| 30. | Von Hertzen et al 2007 | Randomized controlled trial | Eleven gynecological centers in six countries. | Women with single intra-uterine pregnancy less than or equal to 63 days verified by US, requesting termination of pregnancy. | 1) Misoprostol 800 μg sublingual every 3 hours x 3 doses (N=517) vs. 2) Misoprostol 800 μg sublingual every 12 hours x 3 doses (N=516) vs. 3) Misoprostol 800 μg vaginal every 3 hours x 3 doses (N=516) vs. 4) Misoprostol 800 μg vaginal every 12 hours x 3 doses (N=517) |
| 31. | Von | Randomized | Thirteen departments | Women with 63 days | 1) Mifepristone |
| Reference          | Study Type                  | Setting                                                                 | Population                                                                 | Treatment                                                                                       |
|--------------------|-----------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Hertzen et al 2009 | Controlled trial of obstetrics and gynecology in nine countries. | or less gestation verified by ultrasound, requesting termination of pregnancy. | 100 mg + misoprostol 800 μg vaginal 24 hours later (N=545) vs. 2) Mifepristone 100 mg + misoprostol 800 μg vaginal 48 hours later (N=547) vs. 3) Mifepristone 200 mg + misoprostol 800 μg vaginal 24 hours later (N=544) vs. 4) Mifepristone 200 mg + misoprostol 800 μg vaginal 48 hours later (N=545) |
| 32. Von Hertzen et al 2010 | Randomized controlled trial | Fifteen obstetrics/gynecology departments in ten countries. | Women requesting legal termination of pregnancy at a gestation of up to 63 days. | 1) Mifepristone 200 mg + misoprostol 400 μg sublingual 24 hours later (N=751) vs. 2) Mifepristone 200 mg + misoprostol 800 μg sublingual 24 hours later (N=752) vs. 3) Mifepristone 200 mg + misoprostol 400 μg vaginal 24 hours later (N=751) vs. 4) Mifepristone 200 mg + misoprostol 800 μg vaginal 48 hours later (N=752) |
| 33. | Winikoff et al 2008 | Randomized controlled trial | Seven facilities in the United States. | Women seeking medical abortion with pregnancies not exceeding 63 days since the LMP on the day of the medical abortion. Gestational age was determined by LMP, clinical examination, and/or ultrasonography, as needed. | Misoprostol oral 800 μg 24-36 hours after mifepristone (N=482) vs. Misoprostol buccal 800 μg 24-36 hours after mifepristone (N=484) |

**Figures**

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  Inappropriate comparator (18)
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  Inappropriate study population (8)
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Figure 1

PRISMA flow diagram

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