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Review

Medical abortion in the late first trimester: a systematic review☆

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ABSTRACT

Objective: To describe the efficacy, safety, and acceptability of medical abortion in the late first trimester.
Study design: We searched PubMed and Cochrane databases for articles in any language that examined the success of medical abortion at gestational ages (>63 to≤84 days gestation). We sought articles that compared: medical abortion with surgical abortion at this gestational age, combination mifepristone and misoprostol and/or misoprostol alone); different dosages of misoprostol; different routes of misoprostol administration; frequency of dosing; and location of medical abortion (in health care facility vs. outpatient management). Our primary outcome was complete abortion. Data was independently abstracted by two authors, graded for evidence quality, and assessed for risk of bias.
Results: The search strategy returned 3384 articles, nine of which met inclusion criteria. Medical abortion, as compared with surgical abortion, was effective in the late first trimester (94.6% versus 97.9% complete abortion). A combined regimen of mifepristone and misoprostol was significantly more effective than misoprostol alone (90.4 versus 81.6% complete abortion). Complete abortion rates for all regimens investigated ranged from 78.6% to 94.6%. Success rates were higher with repeat dosing of misoprostol both in combination regimens and alone, and with vaginal compared with oral administration for repeat dosing.
Conclusion: A limited body of evidence indicates a range of efficacy of medical abortion in the late first trimester and highlights the need for well-designed trials in this gestational age range.
Implications: This review highlights the need for research focused on the late first trimester to strengthen the body of evidence. The available evidence is limited but offers reassurance that adverse events are rare for later first trimester abortion. Importantly, new research demonstrates that efficacy remains unchanged in the 10th gestational week regardless of whether the medication is taken in a facility or at a woman's home.

1. Introduction

Medical abortion is an effective and acceptable option for abortion care [1–3]. Given the few medical requirements for safe provision of medical abortion drugs, and that the abortion process may generally be managed by the woman, a growing proportion of induced abortions in the United States (US) and internationally are medical abortions [4,5]. Unsafe abortion remains a significant threat to women's lives and health [6–8]. Improved access to medical abortion, including by expanding the gestational ages at which it can safely be used is one strategy to reduce unsafe abortion, particularly where trained surgical providers are limited.

The most effective medical abortion regimen combines mifepristone with misoprostol; however, variation exists in dose, timing and route of administration of the two drugs. A large body of evidence, practice internationally, and recommendations by the World Health Organization (WHO) supports the efficacy of a 200 mg dose of mifepristone, followed by 800 mcg of misoprostol in pregnancies up to 63 days gestational age [9,10] and recent data supports extending its use to 70 days gestation [11]. These protocols are highly effective, with treatment failure occurring in approximately 2–5% of cases [3,9]. Gestational age is known to affect the efficacy of all regimens, with decreasing efficacy after nine weeks gestation [12], which is why regimens recommend routinely repeating misoprostol doses starting in the late first trimester. Home administration of misoprostol has similar effectiveness as clinic administration up to 63 days gestation and is endorsed as a safe and acceptable practice in the WHO guidance [9,10]. Studies of later gestational age ranges would need also to demonstrate similar efficacy, acceptability and rates of adverse events with home administration of medical abortion drugs.

The ideal regimen for medical abortion in the later part of the first trimester has yet to be determined. The objective of this review is to

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synthesize available information on medical abortion during the gestational age range of>63 to≤84 days gestational age. We conducted a review to compare the efficacy, safety and acceptability of medical abortion with surgical abortion; compare evidence on the dosage, route and frequency of misoprostol administration alone or following mifepristone; and compare management of medical abortion at home to within facilities. This systematic review is part of the evidence synthesis for WHO guidance related to the use of medical abortion in the clinical management of abortion care. An improved understanding of the efficacy, safety and acceptability of medical abortion in the later part of the first trimester should strengthen recommendations for medical regimens, and improve the information provided to women considering medical abortion.

2. Materials and methods

We searched PubMed, Embase and Cochrane databases for peer-reviewed articles concerning induced abortion using mifepristone and/or misoprostol late in the first trimester (>63 to≤84 days gestational age) that compared: medical abortion with surgical abortion in this gestational age range; combination regimens of mifepristone misoprostol and/or misoprostol alone (different dosages, routes and frequency of misoprostol administration); and location of medical abortion (in health care facility vs. outpatient management). Our primary outcome of interest was successful abortion, defined as no subsequent intervention needed to achieve complete expulsion of the pregnancy, and a critical outcome reported was ongoing pregnancy. Secondary outcomes included safety issues such as rates of serious adverse events (e.g., transfusion, hospitalization, pelvic infection), patient acceptability (whether patients would opt for the same method again) and satisfaction (whether patients were satisfied with the method), and side effects (e.g., nausea, diarrhea, vomiting, fever).

We searched from database inception through September 2018. To ensure that the primary and secondary outcomes were included in our search, three separate search strategies (comparing medical abortion and surgical management, comparing different drug regimens, comparing location of medical abortion) were developed in collaboration with a research librarian for PubMed, and adapted and combined for Embase and the Cochrane database. We used a combination of subject headings and MESH terms, and key words related to the three key concepts of abortion, gestational age, and mifepristone and misoprostol, as well as Cochrane sensitivity maximizing and precision maximizing filters. See Appendix 1 for full search terms.

Articles were screened first by title and abstract by one author (EE), and then by abstract and full text by two authors (NK and EE). Our inclusion criteria were prospective studies of any design that included a comparative arm, given the small number of randomized trials available, in all languages that reported on any of our outcomes of interest from medical abortion using mifepristone and/or misoprostol between>63 to ≤84 days gestational age. Excluded were studies that investigated gestational age ranges<63 or >84 days; studies that did not disaggregate gestational age and had an average age outside of the scope of this review; and those without a comparative arm meeting the stated inclusion criteria. In some cases, reports were not disaggregated by gestational age range precisely and authors were contacted to ask for these data [13–16]; in cases where disaggregation was not provided, studies were included if they had an average gestational age within the gestational age range of>63 to ≤84 days. Additionally, authors were contacted in one case for clarifications on conflicting numbers presented in their manuscript [17].

Two authors participated in summarizing and systematically assessing the evidence using standard data abstraction forms (NK and EE). The third author (MIR) independently reviewed the abstracted results. Two authors independently assessed the studies for risk of bias using the Cochrane Collaborative's tool (NK and EE) [18]. In case of any disagreement, assessment of a third author was sought (MIR). We planned pooled analyses for each comparison with more than one study reporting under the following conditions: the gestational age range of interest was disaggregated, the medical abortion regimens were comparable and resulting outcomes were reported homogeneously. Where these conditions were not met, a narrative synthesis of the results would be conducted. We used the GRADE approach to assess the quality of evidence related to each of the key outcomes. For assessments of the overall quality of evidence for each outcome that included randomized controlled trials, we downgraded the evidence from "high quality" by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias [19].

3. Results

The search strategy returned a total of 3384 reports after duplicates were removed. We identified nine studies which met inclusion criteria. Of these, six were randomized or partially-randomized trials and three were prospective cohort studies. See Fig. 1 for a Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram [20].

3.1. Medical abortion compared with vacuum aspiration (Table 1)

Two articles meeting inclusion criteria compared vacuum aspiration with medical abortion (200 mg of mifepristone followed by 800 mcg of vaginal misoprostol between 36–48 h later) using a partially-randomized study design [13,21]. In both of these studies, women with a preference between aspiration or medical methods received it; those without a preference were randomized between the two and data from all participants was combined, by method received. Only one of these studies reported on efficacy, finding the proportion of women having a complete abortion following a medical abortion was 94.6% as compared with 97.9% following vacuum aspiration [21], while rates of ongoing pregnancy were 1.5% and 0%, respectively.

Safety outcomes included the following: the Ashok trial reported slightly higher rates of heavy bleeding with medical abortion (2.0% vs 0.8%), as compared with vacuum aspiration, but lower rates of pelvic infection (4.4% vs 8.2%). In the Robson study, there were four transfusions, and 11 suspected pelvic infections, which were not reported by treatment group, and four unplanned hospitalizations among those randomized to medical abortion. Side effects, including nausea, vomiting and diarrhea, were higher among women undergoing medical abortion in both studies. Acceptability was the primary outcome of the Robson study: vacuum aspiration was found to be more acceptable than medical abortion in women randomized to treatment group in both studies, and this preference for surgical treatment was greater at higher gestational ages (Table 1).

Certainty of the evidence for each outcome was assessed using GRADE and ranged from very low to moderate certainty of the evidence. The evidence was downgraded due to indirect evidence, imprecision, and inconsistency. Both studies were deemed at high risk for bias due to flaws in the random sequence generation, introducing the possibility of selection bias, and for selective reporting. It was unclear in both studies, how blinding of outcome assessment and participants was performed, introducing the possibility of detection and performance bias.

3.2. Medical regimens

Eight articles met inclusion criteria, investigating outcomes following different medical regimens of mifepristone and/or misoprostol, dosing or timing (Tables 2–4). Individual dosing for misoprostol ranged from 200 to 800 mcg, and the sublingual, buccal, vaginal and oral routes were all investigated. Frequency of misoprostol dosing ranged from three to 12 h. All studies reported on the efficacy of medical abortion in the late first trimester. Five studies reported on safety, as examined

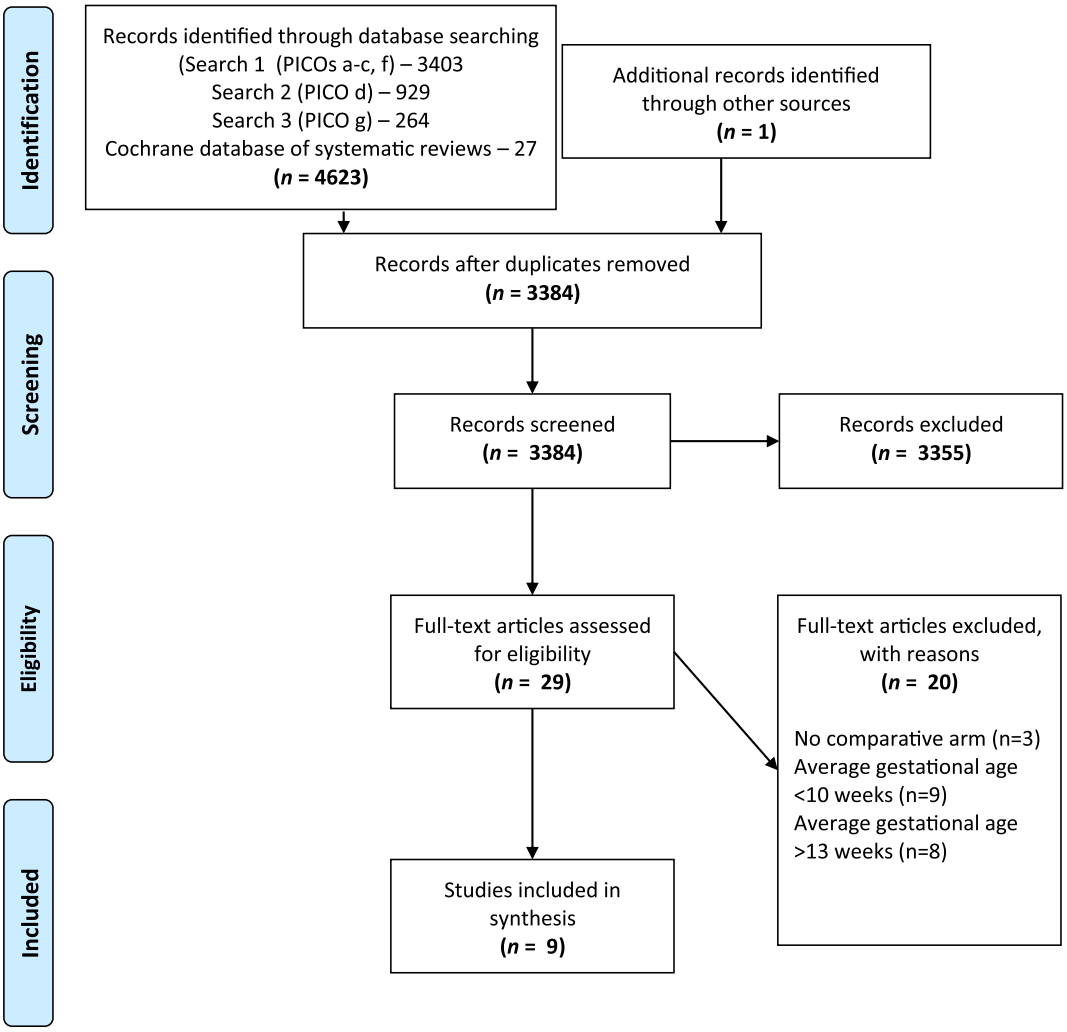

Fig. 1. PRISMA 2009 flow diagram.

by rates of adverse events [14,16,17,22,23], and five presented data on side effects [16,17,22,24,25]. Four studies examined outcomes of patient acceptability or satisfaction [14,17,22,25].

3.2.1. Combination mifepristone/misoprostol compared with misoprostol alone (Table 2)

One small study conducted in Tunisia was identified that compared the combination regimen with misoprostol alone, among women with pregnancies with a gestational age range of 9–12 weeks [17]. Women were randomized to either mifepristone, 200 mg, followed 48 h later by 400 mcg oral misoprostol or to misoprostol alone (800 mcg vaginal administration). After 2 weeks, a quarter of women in both the combination regimen and misoprostol-only groups required a second dose of misoprostol to achieve a complete abortion rate of 80% vs. 78%, respectively; the remaining 19.2% and 32.5% were treated with uterine curettage. Ongoing pregnancy at two-week follow-up was half as common with the combined regimen (9.6%) compared with the misoprostol alone group (18.4%); however, curettage for persistent sac was reportedly no different between the two groups (9.5% vs. 8.1%, respectively). Side effects and acceptability were similar among the two treatment groups.

The study quality was excluded from GRADE due to inability to assess the critical outcome given the apparent discrepancy in reporting, and no reply was received from the authors when contacted for clarification.

3.2.2. Combination mifepristone/misoprostol: Comparing different doses, administrative routes and frequency of misoprostol (Table 3)

Two studies investigated the effect of differences in misoprostol dose and route of administration following mifepristone [14,22]. Hamoda et al. conducted a randomized controlled trial of 340 women presenting for medical abortion with pregnancies up to 13 weeks gestational age. All women received 200 mg of mifepristone, and then were randomized to receive 600 mcg of misoprostol sublingually or 800 mcg vaginally. Misoprostol dosing was repeated at 3 h for all women, and 3 h later a third dose was given if abortion had not occurred. In terms of efficacy between 9–12 weeks gestation, there was no significant difference in the need for surgical evacuation for women in the sublingual and vaginal groups; however, only the sublingual group had ongoing pregnancies (n=2) and were offered surgical treatment while none occurred in the vaginal group. Women receiving misoprostol sublingually, as compared to vaginally, were more likely to experience the side effects of diarrhea (70.5% vs. 52.1%) and shivering among all gestational ages (data not disaggregated). Satisfaction scores were high in both groups (70% vs 68% were satisfied).

Another trial randomized 1112 women presenting for medical abortion between 8–16 weeks gestation in 12 Shanghai hospitals to four treatment groups: 1) 200 mg mifepristone followed by 600 mcg misoprostol vaginally at 24 h, repeated every 3 h; 2) 200 mg mifepristone followed by 600 mcg misoprostol vaginally at 24 h, repeated orally every 3 h; 3) 200 mg mifepristone followed by 600 mcg misoprostol sublingually at 24 h; and 4) 100 mg mifepristone q 24 h for 2 doses

Table 1
Aspiration versus medical abortion

Study	Design	Inclusion criteria	Regimen/ comparison	Sample size	Results	Limitations
Ashok [1], 2002 Scotland Single site	Partial RCT medical versus surgical	Healthy, seeking abortion and eligible for either medical abortion (MA) or vacuum aspiration (VA) - singleton - confirmed by US Those without strong preference were randomized GA 10–13 weeks	Vacuum aspiration under general anesthesia (cervical priming with misoprostol 800 mcg 3 h prior) Mifepristone 200 mg, 36-48 h later 800 mcg PV misoprostol (400 mcg q3 up to 2 doses)	*n*=486 Randomized arm=400 Preference arm=86	**Efficacy** (VA vs MA): Complete abortion 237/242 vs. 192/203 Failed abortion 5/242 vs 11/203 - Ongoing pregnancy 0/242 vs 3/203 Median MA interval 5 h; median doses miso 2 5 h (range 2.00–27.58); dose 2 (range 0–3) **Side effects** (denominator those who had SE) (VA vs MA): Nausea 50/180 vs 128/186 Vomiting 15/180 vs 91/186 Diarrhea 8/180 vs 79/186 **Safety** (up to 8 weeks after) (VA vs MA): Heavy bleeding 2/242 vs 4/203 Transfusion 1/242 vs 0/203 Presumed pelvic infection 17/207 vs 7/158 **Acceptability** ('preference' of VA vs MA): Would have same method in future 76/96 vs 47/67	Partially randomized (those who chose their group appeared similar to randomized in terms of GA, age, etc.) Misoprostol use for cervical priming prior to aspiration (may confound side effects)
Robson, 2009 [2] UK Single site	RCT (combined data with non-randomized prospective cases)	Healthy women able to consent>16 yo seeking abortion GA<14 wk	Vacuum aspiration (6<14 wk) Mifepristone 200 mg, 36-48 h later 800mcg PV miso (q 3 h 400 mcg) up to 4 doses	*n*=1877 Randomized arm=349 Preference arm=1528	**Side effects** (randomized VA vs MA): Nausea 3.3% vs 20.9% (n not provided) Vomiting 2.6% vs 0.8% (n not provided) Diarrhea 0.6% vs 5.3% (n not provided) **Safety** (randomized VA vs MA): Hospitalization 0/187 vs 4/162 Suspected infection 11 cases (unknown groups) Transfusion 4 cases (unknown groups) Failed VA/MA resulting in uterine perforation/laparotomy *n*=1 **Acceptability** ('would you opt for the same method' (randomized VA vs MA): (2 wk after abortion): 94% (*n*=134) vs. 69% (123) Difference between method (VA vs MA) acceptability increases with GA	Data not disaggregated by GA Data (%) presented without denominators

Table 2
Combined mifepristone/misoprostol versus misoprostol alone

Study	Design	Inclusion criteria	Regimen/ comparison	Sample size	Results	Limitations
Dalenda, 2010 [3] Tunisia Single site	RCT	Healthy women, GA confirmed by ultrasound GA 9–12 weeks	Mifepristone 200 mg followed 48 h later by 400 mcg oral miso Misoprostol, 800 mcg, PV	$n=122$ mife +miso=73 miso alone=49	**Efficacy** (mife+miso vs. miso alone): Successful abortion 40/73 vs. 28/49 Success (additional miso dose) 18/19 vs 10/10 Ongoing pregnancy: 7/73 vs 9/49 **Side effects** (mife+miso vs. miso alone): Pain 32/73 vs 35/49 Fever 4/73 vs 2/49 Diarrhea 2/73 vs 0/49 Chills 1/73 vs 0/49 Nausea/vomiting 2/73 vs 2/49 Heavy bleeding 57/73 vs 41/49 **Safety**: no cases of uterine rupture, transfusion **Acceptability** (acceptability of method; mife+miso vs miso alone): 55/73 vs 37/49	Not true randomization (by consultation date) No power calculation No repeat misoprostol in initial regimen

followed by 600 mcg misoprostol vaginally every 12 h [14]. The complete abortion rates among the gestational age group of 8–10 weeks was significantly lower in group 4, at 78.2%, than the other groups (≈93%, ≈89%,≈87%, respectively); ongoing pregnancy rates were similar between groups (2.2–2.9%). Average number of repeated doses was not reported by gestational age range. No differences in complete abortion were found between groups at higher gestational ages. Exact numbers were not provided in the text but extrapolated for this gestational age range from a figure in the report.

One study was excluded from GRADE [14]. For the article by Hamoda, et al., [22] the certainty of the evidence was assessed as very low, with confidence in the direct estimates limited. The study was downgraded due to indirect evidence, imprecision, and inconsistency. The study was deemed at high risk for bias due to inadequate blinding of outcome assessment or participants.

3.2.3. Misoprostol alone: comparing different routes/doses (Table 4)

Three studies compared different misoprostol-only regimens for late first trimester abortion [15,16,23]. A randomized trial of women presenting for medical abortion in Iran with pregnancies up to 16 weeks investigated the effect of differing misoprostol doses [16]. Women with an indication for induced abortion (but without evidence of a failed or threatened abortion) were randomized to either 200 or 400 mcg of misoprostol vaginally every 6 h for up to four doses. Complete abortion rates at 48 h were not significantly different between the two groups (74.5% vs 76%, p=.086); although data were not disaggregated by gestation age, average was about 11 weeks.

A second prospective cohort study conducted in Mozambique compared efficacy of medical abortion with 200 mcg or 400 mcg misoprostol given vaginally every 12 h [23]. Complete abortion rates were low overall at 48 h at which point vacuum aspiration was performed among those incomplete, but higher among women receiving 400 mcg (30%) than 200 mcg (25%). Van Bogaert, et al. compared 400 mcg of sublingual misoprostol followed by 800 mcg of misoprostol vaginally or orally every 8 h among a prospective cohort [15]. Complete abortion rates were higher among the vaginal group when compared with the oral group (93.4% vs 86.9%) with 42% of the women requiring repeat misoprostol. The only factor in a linear regression associated with need for repeat misoprostol doses was increasing gestational age. Rates of ongoing pregnancy were not reported.

Certainty of the evidence for each outcome available ranged from very low to low for the two studies [16,23]. The evidence was downgraded due to indirect evidence, imprecision, and inconsistency. All three studies were judged at high or unclear risk of bias due to incomplete description of blinding of outcome assessment and participants. Additionally, limitations to the randomization and allocation concealment resulted in one study being judged at high risk of bias for both categories [15].

3.2.4. Location of medical abortion: management outside of health facilities (Table 5)

One article investigating the management of abortion outside of health care facilities met inclusion criteria. In a comparative, nonrandomized study conducted in Kazakhstan, investigators compared clinic- based versus at home administration of mifepristone (200 mg) in women with pregnancies up to 70 days of gestational age [26]. Women were given the option to take mifepristone in the clinic or at home followed by home-administered sublingual misoprostol, 600 mcg. Out of a total sample of 290 women, 16 had pregnancies between 64 and 70 days gestational age. Ten of these took mifepristone at home, and six in the clinic. Most women (15/16) had a successful medical abortion; there was one ongoing pregnancy (1/16). There were no serious adverse events. Chills, diarrhea and nausea were the most common side effects. Overall, satisfaction rates were high among both groups with 98.4% of the home group and 99.0% of the clinic group reporting being very satisfied or satisfied.

Table 3
Combined mifepristone misoprostol (comparisons of different regimens)

Study	Design	Inclusion criteria	Regimen/ comparison	Sample size	Results	Limitations
Hamoda 2005 [4] Scotland Single site	RCT	Healthy women aged>16 yo with singleton pregnancy, confirmed by US GA<13 weeks	Mifepristone 200 mg followed 36-48 h later by: Misoprostol 600 mcg SL, q3h Misoprostol 800 mcg PV, q3h	*n*=340 SL=171 VL=169	**Efficacy 9–12 w** (600mcg SL vs. 800 mcg VL): Complete abortion 102/105 vs 84/87 Failed abortion 3/105 vs 3/87 -ongoing pregnancy 2/105 vs 0/87 **Side effects** (SL vs VL—all GA): Nausea 115/144 vs 113/146 Vomiting 104/148vs 88/144 Diarrhea 105/149 vs 74/142 **Safety** (SL vs VL- all GA): Pelvic infection 3/154 vs 2/144 Hemorrhage 2/154 vs. 0/144 - Transfusion 1/154 vs 1/144 **Satisfaction** (satisfied, dissatisfied, don't know) (SL vs. VL—all GA): 108/154 vs 98/144	3 women required additional miso dose: unclear where accounted for in the data No blinding Only efficacy data disaggregated by gestational age
Chen, 2013 [5] China, 12 centers	RCT	Healthy, 18–40 yo women with singleton pregnancy, GA confirmed by US GA 8–16 weeks	Mifepristone 200 mg followed 24 h later by: 1. 600 mcg PV miso, q 3 h 2. 600 mcg PV miso, q3h oral 3. 600 mcg oral miso, q3h 4. Mifepristone 100 mg, q 24 h x2 followed 24 h later by	*n*=1112 Group 1=271 Group 2=277 Group 3=285 Group 4=279	**Efficacy**: Complete abortion (8–10 weeks): Groups 1–3 significantly more effective (about 90%) than Group 4 (about 78.2%)* Complete abortion (11–12 weeks): No differences between groups *data extracted from a figure	88 women excluded after randomization (dosing interval not respected/ one woman hypertensive) Data not extrapolated by gestational age range No blinding

Table 4
Misoprostol alone (varying regimens)

Study	Design	Inclusion criteria	Regimen/ comparison	Sample size	Results	Limitations
Khazardoost, 2007 [6] Iran Single site	RCT	Women with indication for abortion (fetal malformation, maternal health, failed pregnancy) and closed os GA<16 weeks	Misoprostol, 200 mcg PV q6 x4 Misoprostol, 400 mcg PV q 6 x4	*n*=100 200mcg=50 400 mcg=50	Data not disaggregated by GA (200mcg vs. 400mcg): mean GA 82d vs. 77d **Efficacy** (200 vs 400 mcg): Complete abortion (within 48 h) 35/47 vs. 38/50 Failed abortion 3/50 vs 0/50 **Side effects** (200mcg vs 400 mcg): Nausea 0/50 vs 2/50 Vomiting 2/50 vs 2/50 Fever 5/50 vs 14/50 Diarrhea 0/50 vs 1/50	Voluntary participation not clear No power calculation No blinding No disaggregation by gestational age Women enrolled had medical indication for abortion
Vanbogaert, 2010 [7] South Africa Single site	Prospective cohort	Women seeking abortion, GA confirmed by US GA (first or second trimester)	Misoprostol, 400mcg SL, then 800 mcg po or VL (q8 x6)	*n*=454 VL=177 Oral=277	**Efficacy** (VL vs oral with mean GA 10.4 wk): Complete abortion 71/76 vs. 93/107 Complete abortion after first dose 59/76 vs 58/107	Primary outcome was whether anthropomorphic characteristics correlated with misoprostol response
Bugalho, 1996 [8] Mozambique Single site	Prospective cohort	Healthy normotensive, seeking abortion between 18–35 yo, GA confirmed by US GA 35–77 days	Misoprostol, 200 mcg PV q 12 x4 Misoprostol, 400 mcg PV q 12 x4	*n*=234 200 mcg=101 400 mcg=133	**Efficacy** 8–11 wk.(200 vs 400 mcg): Complete abortion 14/57 vs. 14/46 *reporting results where GA disaggregated	Allocation to treatment groups not specified Side effects not presented by GA Outcome assessed at 48 h

Table 5
Clinic versus home use of medical abortion

Study	Design	Inclusion criteria	Regimen/ comparison	Sample size	Results	Limitations
Platais, 2016 [9] Kazakhstan (3 sites)	Prospective comparative trial	Women eligible for medical abortion (GA by LMP/clinical exam +/− US) GA<70 days	Mifepristone, 200 mg followed 24-48 h later by 600 mcg miso SL Comparison: all medications at home versus mifepristone in clinic	*n*=290 Home=185 Clinic=105	**Efficacy** (not disaggregated by home/clinic use): Complete abortion: 16/17(57–63 d) vs. 15/16 (64–70 d) Ongoing pregnancy 0/17 vs 1/16 **Safety:** no serious adverse events **Satisfaction** (all MA at home vs. mife in clinic): Satisfied/very satisfied 179/182 vs 101/103 **Acceptability** (Choose future location of mife at home): 168/182 vs 73/103	3 received additional misoprostol Side effects not disaggregated by GA or home/ clinic use Small sample size for 64–70 day gestational age range

1. Ashok, P.W., et al., *A randomized comparison of medical abortion and surgical vacuum aspiration at 10–13 weeks gestation.* Hum Reprod, 2002. **17**(1): p. 92–8.
2. Robson, S.C., et al., *Randomized preference trial of medical* versus *surgical termination of pregnancy less than 14 weeks' gestation (TOPS).* Health Technol Assess, 2009. **13**(53): p. 1–124, iii-iv.
3. Dalenda, C., et al., *Two medical abortion regimens for late first-trimester termination of pregnancy: a prospective randomized trial.* Contraception, 2010. **81**(4): p. 323–7.
4. Hamoda, H., et al., *A randomized controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation.* Bjog, 2005. **112**(8): p. 1102–8.
5. Chen, Q.-j., et al., *Mifepristone in Combination with Misoprostol for the Termination of Pregnancy at 8–16 Weeks' Gestational Age: A Multicentre Randomized Controlled Trial.* Journal of Reproduction and Contraception, 2013. **24**(2): p. 101–113.
6. Khazardoost, S., S. Hantoushzadeh, and M.M. Madani, *A randomized trial of two regimens of vaginal misoprostol to manage termination of pregnancy of up to 16 weeks.* Aust N Z J Obstet Gynaecol, 2007. **47**(3): p. 226–9.
7. van Bogaert, L.J. and A. Misra, *Anthropometric characteristics and success rates of oral or vaginal misoprostol for pregnancy termination in the first and second trimesters.* Int J Gynaecol Obstet, 2010. **109**(3): p. 213–5.
8. Bugalho, A., et al., *Evaluation of the effectiveness of vaginal misoprostol to induce first trimester abortion.* Contraception, 1996. **53**(4): p. 244–6.
9. Platais, I., et al., *Prospective study of home use of mifepristone and misoprostol for medical abortion up to 10 weeks of pregnancy in Kazakhstan.* Int J Gynaecol Obstet, 2016. **134**(3): p. 268–71.

Table 6
Risk of bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessment (detection bias) (all outcomes)	Blinding participants and personnel (performance bias)	Incomplete outcome data (attrition bias) (all outcomes)	Selective reporting (reporting bias)	Other sources of bias
Ashok, 2002	High	High	Unclear	Unclear	Low	High	High
Robson, 2009	High	Unclear	Unclear	Unclear	High	High	Unclear
Hamoda, 2005	Low	Low	High	High	Low	Low	Unclear
Chen, 2013	Low	Low	Unclear	High	Low	Low	High
Khazardoost, 2007	Low	Unclear	High	High	Low	Low	High
van Bogaert, 2010	High	High	Unclear	Unclear	Low	Low	Unclear
Bugalho, 1996	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Plantais, 2015	High	High	Unclear	Unclear	Low	High	Unclear

Certainty of the evidence for each outcome was assessed using GRADE and was very low. The evidence was downgraded due to indirect evidence, imprecision, and inconsistency. Risks of bias for this study included limitations to the randomization scheme, limited allocation concealment (introducing possibility of selection bias), and selective reporting of outcomes.

4. Discussion

Available evidence of efficacy and safety of medical abortion in the late first trimester is limited and highlights the need for well-designed trials in this gestational age range. Complete abortion rates for all regimens investigated ranged from 78.6% to 94.6%. Success rates were in the higher range when misoprostol dosing was repeated, both in combination regimens and alone, and when vaginal compared with oral administration was used. Ongoing pregnancy rates were lowest with the combination regimen, mifepristone and misoprostol. This limited body of evidence offers reassurance that adverse events are rare during medical abortion in the late first trimester.

Overall, safety issues reported with medical abortion in the late first trimester were rare. An increased risk of heavy bleeding appears more likely with medical abortion as compared with vacuum aspiration [21] and appears to be greater as gestational age increases [25]. As with most studies of abortion, overall satisfaction and acceptability were high among participants; one exception may be for women randomized between methods, vacuum aspiration was significantly more acceptable than medical abortion [21].

Importantly, new research is investigating the safe expansion of abortion management into a woman's home in this gestational age range. Although only one prospective study compared home use of medical abortion with clinic administration of mifepristone in gestations up to 70 days and was included in this review, other research is supportive. Two comparative, prospective studies, which had a comparison arm outside the gestational age range of this review and did not meet inclusion criteria, investigated the efficacy of medical abortion between 64–70 days compared with 57–63 days. One study with a total of 714 women found no significant difference in abortion efficacy between groups, with 94.8% and 91.9% (RR 0.79 CI 0.61–1.04) reporting complete abortions in the earlier and later gestational age groups, respectively [24]. The rate of surgical intervention for excessive/prolonged bleeding was significantly greater for the later gestational age (0.5% in 57–63 days versus 2.5% in 64–70 days). A similarly-designed study in the US enrolled 729 women using 200 mg mifepristone followed 24–48 h later by 800 mcg buccal misoprostol [25]. Rates of successful abortion did not differ between the two groups (93.5% vs 92.8%, respectively) nor did ongoing pregnancy (3.1% vs 3.0%). There were no differences in major adverse events. These studies demonstrate that efficacy remains unchanged in the 10th gestational week regardless of whether the mifepristone and misoprostol are taken in a facility or at a woman's home. Whether home administration at gestations later than 70 days has similar efficacy, adverse events and acceptability is a subject for future research.

Interpretation of these data should take into consideration some key limitations of existing evidence (Table 6). The main outcome, efficacy, as measured by complete abortion, was evaluated differently in terms of timing and criteria across studies, and not all studies reported on rates of ongoing pregnancy, which increases the possibility of performance or detection bias. Some studies repeated misoprostol administration based on provider discretion without reporting treatment group and efficacy [22,26]. Few studies were randomized using standard random sequence generation and allocation concealment, which introduces the possibility of selection bias [15,17,21,23,26]. Studies varied in assessment and timing of the outcome of abortion, which makes comparing outcomes challenging and a lack of blinding may lead to detection bias. Data were not always clearly disaggregated by gestational age and findings from these studies risk reflecting outcomes skewed towards earlier gestations [14–16,22,23,26] . Key differences in how acceptability to women was measured and reported limit the generalizability of findings and are likely most useful in comparing satisfaction between treatment groups within the study.

Expanding the gestational ages at which medical abortion can be safely offered can increase access to quality abortion services. Current evidence supports the home use of mifepristone and misoprostol up to 70 days gestation, and emphasizes the need for routine, repeated misoprostol dosing beyond 70 days. Although medical abortion has great potential that is only becoming realized, uterine aspiration methods should remain an important option for women, as it is associated with high satisfaction and possibly with lower rates of adverse events of excessive bleeding. Further research of medical abortion in the late first trimester should aim to determine whether the gestational age range for home use is appropriate beyond 70 days gestation, and to investigate whether efficacy can be improved with misoprostol-only regimens by increasing the dose or timing interval; however, future research should be carefully designed to avoid introducing the most common biases we encountered in the literature, namely: selection, detection and performance biases. Ensuring access to safe abortion services is an important strategy to reduce maternal morbidity and mortality. Increasing the gestational age at which medical abortion is offered is one way to safely increase access to a critical health service.

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Appendix 1. Search strategy

Final Search – PICO d PUBMED			
Randomized controlled trials comparing 1st tri medical abortion with mife/miso and surgical abortion			
Final Search – PICOs a-c, f PUBMED			
Randomized controlled trials of 1st tri medical abortion with mife/miso			
1	Abortion	Abortion, induced[MeSH] OR termination of pregnancies[tiab] OR termination of pregnancy[tiab] OR pregnancy termination[tiab] OR abortion[tiab] OR menstrual regulation[tiab] OR termination of pregnancies[ot] OR termination of pregnancy[ot] OR pregnancy termination[ot] OR abortion[ot] OR menstrual regulation[ot]	69,536
2	Gestational age	Gestational age[MeSH] OR Pregnancy[MeSH] OR Pregnancy Trimester, First[MeSH] OR Pregnancy trimesters[MeSH] OR first trimester[tiab] OR Gestation* [tiab] OR Last menstrual period[tiab] OR 70 days[tiab] OR first trimester[ot] OR Gestation*[ot] OR Last menstrual period[ot] OR 70 days[ot]	921,695
3	Mife/miso	misoprostol[MeSH] OR mifepristone[MeSH] OR misoprostol[tiab] OR mifepristone[tiab] OR RU-486[tiab] OR RU486[tiab] OR misoprostol[ot] OR mifepristone [ot] OR RU-486[ot] OR RU486[ot]	11,927
4		1 AND 2 AND 3	2412
1	Abortion	Abortion, induced[MeSH] OR termination of pregnancies[tiab] OR termination of pregnancy[tiab] OR pregnancy termination[tiab] OR abortion[tiab] OR menstrual regulation[tiab] OR termination of pregnancies[ot] OR termination of pregnancy[ot] OR pregnancy termination[ot] OR abortion[ot] OR menstrual regulation[ot]	69,536
2	Gestational age	Gestational age[MeSH] OR Pregnancy[MeSH] OR Pregnancy Trimester, First[MeSH] OR Pregnancy trimesters[MeSH] OR first trimester[tiab] OR Gestation* [tiab] OR Last menstrual period[tiab] OR 70 days[tiab]	921,695

(*continued*)

Final Search – PICO d PUBMED			
Randomized controlled trials comparing 1st tri medical abortion with mife/miso and surgical abortion			
Final Search – PICOs a-c, f PUBMED			
Randomized controlled trials of 1st tri medical abortion with mife/miso			
		OR first trimester[ot] OR Gestation*[ot] OR Last menstrual period[ot] OR 70 days[ot]	
3	Mife/miso	misoprostol[MeSH] OR mifepristone[MeSH] OR misoprostol[tiab] OR mifepristone[tiab] OR RU-486[tiab] OR RU486[tiab] OR misoprostol[ot] OR mifepristone [ot] OR RU-486[ot] OR RU486[ot]	11,927
4	Surgical abortion	(Dilatation and curettage[MeSH] OR Vacuum Curettage[MeSH] OR Surgical abortion[tiab] OR vacuum aspiration[tiab] OR Curettage[tiab] OR Surgical termination of pregnancy[tiab] OR Dilatation and evacuation[tiab] OR Dilation and evacuation[tiab] OR Suction aspiration[tiab] OR Aspiration abortion [tiab] OR Suction curettage[tiab] OR Vacuum curettage[tiab] OR Surgical abortion[ot] OR vacuum aspiration[ot] OR Curettage[ot] OR Surgical termination of pregnancy [ot] OR Dilatation and evacuation[ot] OR Dilation and evacuation[ot] OR Suction aspiration[ot] OR Aspiration abortion [ot] OR Suction curettage[ot] OR Vacuum curettage[ot])	13,621
5		1 AND 2 AND 3 AND 4	682
Final Search – PICO g PUBMED			
Studies comparing management of 1st tri medical abortion inside of and outside of health facilities			
1	Abortion	Abortion, induced[MeSH] OR termination of pregnancies [tiab] OR termination of pregnancy[tiab] OR pregnancy termination[tiab] OR abortion[tiab] OR menstrual regulation[tiab] OR termination of pregnancies[ot] OR termination of pregnancy[ot] OR pregnancy termination[ot] OR abortion[ot] OR menstrual regulation[ot]	69,536
2	Mife/miso	misoprostol[MeSH] OR mifepristone[MeSH] OR misoprostol[tiab] OR mifepristone[tiab] OR RU-486[tiab] OR RU486[tiab] OR misoprostol[ot] OR mifepristone[ot] OR RU-486[ot] OR RU486[ot]	11,927
3	Home use	Self Administration[MeSH] OR Self Care[MeSH:NoExp] OR Self medication[MeSH] OR informal sector[MeSH] OR home use[tiab] OR home administ*[tiab] OR home manage*[tiab] OR self administ*[tiab] OR self induc*[tiab] self manage*[tiab] OR informal sector[tiab] OR at home[tiab] OR home use[ot] OR home administ*[ot] OR home manage*[ot] OR self administ*[ot] OR self induc*[ot] OR self manage*[ot] OR informal sector[ot] OR at home[ot]	52,449
4		1 AND 2 AND 3	119
Final Search – PICOs a-c, f EMBASE SEARCH 1			
Randomized controlled trials of 1st tri medical abortion with mife/miso			
1	Abortion	'induced abortion'/de OR 'termination of pregnancies':ti,ab,kw OR 'termination of pregnancy':ti,ab,kw OR 'pregnancy termination':ti,ab,kw OR 'abortion':ti,ab,kw OR 'menstrual regulation':ti,ab,kw	77,587
2	Gestational age	'gestational age'/exp. OR 'gestational age' OR 'pregnancy'/exp. OR 'pregnancy' OR 'first trimester pregnancy'/exp. OR 'first trimester pregnancy' OR 'first trimester':ti,ab,kw OR gestation*:ti,ab,kw OR 'last menstrual period':ti,ab,kw OR '70 days':ti,ab,kw	1,009,808
3	Mife/miso	'misoprostol'/exp. OR 'misoprostol' OR 'mifepristone'/exp. OR 'mifepristone' OR misoprostol:ti,ab,kw OR mifepristone:ti,ab,kw OR 'ru 486':ti,ab,kw OR ru486:ti,ab,kw	22,569
4		1 AND 2 AND 3 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	1002
Final Search – PICO d EMBASE SEARCH 2			
Randomized controlled trials comparing 1st tri medical abortion with mife/miso and surgical abortion			
1	Abortion	'induced abortion'/de OR 'termination of pregnancies':ti,ab,kw OR 'termination of pregnancy':ti,ab,kw OR 'pregnancy termination':ti,ab,kw OR 'abortion':ti,ab,kw OR 'menstrual regulation':ti,ab,kw	77,587

(*continued*)

Final Search – PICO d EMBASE SEARCH 2			
Randomized controlled trials comparing 1st tri medical abortion with mife/miso and surgical abortion			
2	Gestational age	'gestational age'/exp. OR 'gestational age' OR 'pregnancy'/exp. OR 'pregnancy' OR 'first trimester pregnancy'/exp. OR 'first trimester pregnancy' OR 'first trimester':ti,ab,kw OR gestation*:ti,ab,kw OR 'last menstrual period':ti,ab,kw OR '70 days':ti,ab,kw	1,009,808
3	Mife/miso	'misoprostol'/exp. OR 'misoprostol' OR 'mifepristone'/exp. OR 'mifepristone' OR misoprostol:ti,ab,kw OR mifepristone:ti,ab,kw OR 'ru 486':ti,ab,kw OR ru486:ti,ab,kw	22,569
4	Surgical abortion	'dilatation and curettage'/exp. OR 'dilatation and curettage' OR 'dilation and evacuation'/exp. OR 'dilation and evacuation' OR 'surgical abortion':ti,ab,kw OR 'vacuumaspiration':ti,ab,kw OR curettage:ti,ab,kw OR 'surgical termination of pregnancy':ti,ab,kw OR 'dilatation and evacuation':ti,ab,kw OR 'dilation and evacuation':ti,ab,kw OR 'suction aspiration':ti,ab,kw OR 'aspiration abortion':ti,ab,kw OR 'suction curettage':ti,ab,kw OR 'vacuum curettage':ti,ab,kw	15,179
5		1 AND 2 AND 3 AND 4 [embase]/lim NOT ([embase]/lim AND [medline]/lim)	247
Final Search – PICO g EMBASE SEARCH 3			
Studies comparing management of 1st tri medical abortion inside of and outside of health facilities			
1	Abortion	'induced abortion'/de OR 'termination of pregnancies':ti,ab,kw OR 'termination of pregnancy':ti,ab,kw OR 'pregnancy termination':ti,ab,kw OR 'abortion':ti,ab,kw OR 'menstrual regulation':ti,ab,kw	77,587
2	Mife/miso	'misoprostol'/exp. OR 'misoprostol' OR 'mifepristone'/exp. OR 'mifepristone' OR misoprostol:ti,ab,kw OR mifepristone:ti,ab,kw OR 'ru 486':ti,ab,kw OR ru486:ti,ab,kw	22,569
3	Home use	'Drug self administration'/de OR 'self medication'/de OR 'informal sector'/de OR 'home use':ti,ab,kw OR 'home administ*':ti,ab,kw OR 'home manage*':ti,ab,kw OR 'self administ*':ti,ab,kw OR 'self induc*':ti,ab,kw OR 'self manage*':ti,ab,kw OR 'informal sector':ti,ab,kw OR 'at home':ti,ab,kw	150,335
4		1 AND 2 AND 3 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	145

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