Contraception: X 2 (2020) 100037

Contents lists available at ScienceDirect

Contraception: X

journal homepage: https://www.journals.elsevier.com/conx

Medical regimens for abortion at 12 weeks and above: a systematic review and meta-analysis☆,☆☆

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ARTICLE INFO

Article history:
Received 3 February 2020
Received in revised form 3 August 2020
Accepted 5 August 2020
Available online xxxx

Keywords:
Medical abortion
Mifepristone
Misoprostol
Second trimester

ABSTRACT

Background: Mifepristone and misoprostol are recommended for second-trimester medical abortion, but consensus is unclear on the ideal regimen.
Objectives: The objectives were to systematically review randomized controlled trials (RCTs) investigating efficacy, safety and satisfaction of medical abortion at ≥12 weeks' gestation.
Data sources: We searched PubMed, Popline, Embase, Global Index Medicus, Cochrane Controlled Register of Trials and International Clinical Trials Registry Platform from January 2008 to May 2017.
Study eligibility, participants and interventions: We included RCTs on medical abortion at ≥12 weeks' gestation using mifepristone and/or misoprostol. We excluded studies with spontaneous abortion, fetal demise and mechanical cervical ripening and those not reporting ongoing pregnancy (OP).
Study appraisal and synthesis methods: After extracting prespecified data and assessing risk of bias in accordance with the Cochrane handbook, we used Revman5 software to combine data and GRADE to assess certainty of evidence.
Results: We included 43 of the 1894 references identified. Combination mifepristone–misoprostol had lower rates of OP [risk ratio (RR) 0.12, 95% confidence interval (CI) 0.04–0.35] vs. misoprostol only. A 24-h interval between mifepristone and misoprostol had lower OP rate at 24 h than simultaneous dosing (RR 3.13, 95% CI 1.23–7.94). Every 3-h dosing had lower OP rate at 48 h (RR 0.39, 95% CI 0.17–0.88).
Limitations: Direct comparisons of buccal misoprostol to sublingual or vaginal routes after mifepristone were limited. Evidence from clinical trials on how to best manage women with prior uterine incisions was lacking.
Conclusion: Our analysis supports the use of mifepristone 200 mg 1 to 2 days before misoprostol 400 mcg vaginally every 3 h at ≥12 weeks' gestation.
Implications: Where available, providers should use mifepristone plus misoprostol for second-trimester medical abortion. Vaginal misoprostol appears to be most efficacious with fewest side effects, but sublingual and buccal routes are also acceptable.

1. Introduction

Of the nearly 56 million abortions that occur annually worldwide [1], about 10% occur in the second trimester [2]. Second-trimester abortions can be safely performed medically or surgically with procedure type dependent on patient preference, provider skillset or country-specific practices. Second-trimester medical abortions typically occur in the inpatient setting. Prostaglandin analogues, such as misoprostol, are the most commonly used medications to induce abortion. The World Health Organization (WHO) and the Society of Family Planning both recommend that misoprostol be used with mifepristone, where available, for second-trimester medical abortion [3,4]. Misoprostol can be administered via a variety of routes (vaginal, sublingual, buccal, rectal, oral), doses (typically 200 to 800 mcg) and dosing frequencies. Some providers use a misoprostol loading dose, a one-time higher dose of misoprostol, at the initiation of the abortion.

A 2011 Cochrane review by Wildschut et al. evaluated medical abortion regimens at 12 to 28 weeks of gestation and concluded that the optimal regimen was mifepristone plus misoprostol vaginally every 3 h [5]. The WHO's 2012 guidelines on safe abortion recommend mifepristone

☆ This work was supported by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), World Health Organization, Department of Reproductive Health and Research.
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https://doi.org/10.1016/j.conx.2020.100037

200 mg orally 36 to 48 h before repeated doses of misoprostol 400 mcg vaginally or sublingually every 3 h for medical abortion at 12 to 24 weeks of gestation [4]. Since both the WHO guidelines and Cochrane review were published, the body of evidence on second-trimester medical abortion has continued to grow, with increasing focus on mifepristone as access to this medication has expanded. Our review aims to evaluate the efficacy, safety and satisfaction of various misoprostol regimens with or without mifepristone for medical abortion at ≥12 weeks of gestation to contribute to the WHO's update of its safe abortion guidelines.

2. Methods

2.1. Data sources and searches

We searched PubMed, Embase, Popline, Global Index Medicus, Cochrane Controlled Register of Trials and the International Clinical Trials Registry Platform for all articles published between January 2008 and May 2017 on induced abortion at 12 weeks of gestation or greater. We chose January 2008 as the start date to identify eligible publications not included in the 2011 Cochrane Review by Wildschut et al. [5]. Complete search terms, found in Supplement 1, included "abortion," "mifepristone," "misoprostol" and "randomized clinical trial" and were the same as those used by Wildshut et al. We evaluated the articles that Wildshut et al. considered for their 2011 review (which included studies from database inception to 2009) and included those that met inclusion for our review [5]. We reviewed reference lists of included articles to identify additional publications. We contacted investigators in an attempt to retrieve unpublished data when applicable.

2.2. Study selection

Two reviewers (K.W. and A.B.) independently reviewed references and abstracts for inclusion using the Covidence® tool [6]. We reviewed the full text of all potentially relevant articles. We included randomized clinical trials reporting a mean gestational age of ≥12 weeks of gestation that compared one of the following methods of induced abortion: (1) combination mifepristone–misoprostol (i.e., "combination regimens") vs. misoprostol only, (2) various dosages and timings in combination regimens, (3) various routes of misoprostol in combination regimens, (4) various dosages and timings in misoprostol-only regimens and (5) various routes in misoprostol-only regimens. We excluded studies with other designs or those in which participants had spontaneous fetal demise, spontaneous abortion (incomplete, threatened or missed abortion), septic abortion or preinduction mechanical cervical preparation (e.g., osmotic cervical dilators) and studies not reporting our primary outcome. Conflicts regarding inclusion were resolved through discussion to meet consensus.

2.3. Data extraction and quality assessment

Three researchers worked in pairs to independently extract data and perform risk of bias (RoB) assessment for all outcomes in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [7]. We attempted to obtain study protocols to assess selective outcome reporting. The third reviewer compared quality assessments and extracted data to obtain consensus.

2.4. Data synthesis and analysis

Our primary outcome was ongoing pregnancy (i.e., failure to expel pregnancy) within 24 and 48 h. We evaluated secondary outcomes of serious adverse events (SAEs), defined as hospitalization postabortion, blood transfusion, need for postevacuation surgery or death; participant satisfaction (with intervention arm or with route of misoprostol); abortion completion without the need for surgical intervention; time to pregnancy expulsion; and side effects (bleeding, pain, vomiting, diarrhea). If a study had a mean gestational age of ≥12 weeks but included participants with a gestational age below 12 weeks, we extracted disaggregated data on the subpopulation at ≥12 weeks' gestation if available. Otherwise, we reported all data together. We attempted to contact study authors in order to verify key study characteristics and to obtain missing numerical outcome data as necessary. If unable to make contact, we described the data as "not reported" and did not impute the missing values. For studies with more than two arms, we extracted data from arms meeting our criteria.

We used the Revman5 software tool to conduct analyses [8]. We analyzed dichotomous outcome data based on the number of events and the number of women assessed in the groups; we then calculated the risk ratio (RR) and 95% confidence interval (CI) (Mantel–Haenszel, random effects). We analyzed continuous outcome data based on the mean, standard deviation (SD) and number of women assessed for both the comparison groups; we then calculated the mean difference (MD) and 95% CI (inverse variance). Effect estimates reported as median (range), median with interquartile range (IQR) or mean (95% CI) were converted to mean with SD. Effect estimates reported as median (95% CI) were converted to mean with SD by identifying mean as the middle of the 95% CI and SD as (95% CI)/3.92.

We examined study populations, interventions and outcomes to assess for heterogeneity and determine whether the studies were similar enough to be pooled in a meta-analysis. We assessed the degree of statistical heterogeneity by visual examination of the scatter of effect estimates on forest plots and by using the χ^2 and I^2 statistics [9]. We prepared forest plots for our primary outcome for comparisons including two or more trials.

Two researchers assessed the certainty of the evidence (high, moderate, low and very low) using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) following recommendations of the Cochrane Handbook [7] in GRADEpro software [10]. We resolved disagreements on certainty ratings by discussion. Justifications for decisions to down- or upgrade are presented in footnotes of the tables. For each comparison, tabulated results for main and secondary outcomes are available online (Appendices 4–8).

We initiated this systematic review as part of the evidence syntheses for the WHO's medical abortion guidance [11], which is a focused update of the *Safe abortion: technical and policy guidance for health systems* [4]. We followed the WHO principles for guideline development [12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. We registered this review prospectively with PROSPERO (PROSPERO 2017 CRD42017076899 available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017076899).

3. Results

We identified 1894 unique references, assessed 166 full-text articles and included 43 trials in this systematic review and meta-analysis (Fig. 1). Investigators performed studies in 23 countries and 6 UN regions (Table 1): Africa (1), Eastern Mediterranean (1), Europe (9), Americas (3), Southeast Asia (3) and Western Pacific (6), with 12 being in low- or middle-income countries [13]. All trials took place in the inpatient setting. Gestational age in studies ranged from 8 to 28 weeks of gestation. Three studies included subpopulations of 8 to <12 weeks of gestation [14–16]. We were unable to report the percentage of our review population that was at <12 weeks of gestation due to incomplete reporting of gestational age groups by authors and thus were also unable to analyze data without this lower gestational subgroup. Two studies included women who underwent induced fetal demise immediately before abortion [17,18]. Nine studies included a total of 172 women with a scarred uterus [16,18–25]. In three studies, women with a scarred uterus comprised 22% of the population [18,21,22].

Risk of bias assessments are available in Supplements 2 and 3. Thirty-six (83.7%) trials reported the method of randomization. Authors adequately reported allocation concealment in 24 (55.8%) trials. Single or double blinding occurred in 11 (25.6%) trials. Selective outcome reporting bias was adequately reported in 7 (16.3%) trials, and incomplete outcome reporting RoB was low in 28 (65.1%) trials.

3.1. Mifepristone–misoprostol vs. misoprostol only

Seven trials with 1026 total subjects compared combination mifepristone–misoprostol to misoprostol only (Fig. 2, Supplements 4 and 5) [18,26–31]. The combination regimen resulted in lower rates of ongoing pregnancy at 24 h (RR 0.12, 95% CI 0.04–0.35) and 48 h (RR 0.22, 95% CI 0.08–0.60 at 48 h, low certainty evidence). Authors of these trials only reported one SAE; thus, we could not evaluate this outcome further. Combination regimens had shorter mean time to pregnancy expulsion (5.87 h shorter, range 3.96–7.78 h shorter) and higher rates of complete abortion at 24 h (RR 1.42, 95% CI 1.01–1.99) and 48 h (RR 1.13, 95% CI 1.01–1.26). We found no difference in satisfaction (high certainty evidence). Evidence was of moderate certainty except where specified.

3.2. Combination mifepristone–misoprostol regimens

3.2.1. Mifepristone–misoprostol dosing intervals

Two trials with 646 total subjects compared simultaneous mifepristone–misoprostol dosing to a minimum 24-h interval (Fig. 3, Supplements 6A and 7A) [32,33]. Simultaneous dosing resulted in higher rates of ongoing pregnancy at 24 h (RR 3.13, 95% CI 1.23–7.94, low certainty evidence) and higher rates of diarrhea (RR 1.64, 95% CI 1.34–2.01, moderate certainty evidence).

Four trials with 830 total subjects compared a 24-h interval to a 48-h interval (Fig. 4, Supplements 6B and 7B) [16,24,25,34]. The 24-h regimen resulted in higher rates of vomiting (RR 1.38, 95% CI 1.08–1.76) and diarrhea (RR 1.47, 95% CI 1.01–2.14), both with moderate certainty evidence. We found no difference in ongoing pregnancy rates.

3.2.2. Mifepristone dosage

One trial with 70 subjects compared 200 mg vs. 600 mg of mifepristone before misoprostol (Supplements 6C and 7C) [35]. We found no differences in any outcomes.

3.2.3. Misoprostol loading dose

One trial with 562 subjects evaluated mifepristone plus a misoprostol 600-mcg loading dose vs. no loading dose (Supplements 6D and 7D) [14]. The group without a loading dose had a lower rate of vomiting (RR 0.56, 95% CI 0.34–0.91, low certainty evidence). We found no differences in ongoing pregnancy rates.

3.2.4. Variations of mifepristone–misoprostol regimens

In one trial with 550 subjects, group A received mifepristone 200 mg orally 24 h before misoprostol 600 mcg every 3 h, and group B received mifepristone 100 mg orally 48 and 24 h before misoprostol 600 mcg every 12 h (Supplements 6E and 7E) [14]. Group A had lower rates of satisfaction (RR 0.87, 95% CI 0.81–0.93) and higher rates of pain (RR 1.24, 95% CI 1.03–1.50), both with moderate certainty evidence. We found no differences in ongoing pregnancy rates.

In another trial with 327 subjects, 48 h after mifepristone, group A received misoprostol 400 mcg orally every 3 h, and group B received a loading dose of misoprostol 600 mcg vaginally followed by misoprostol

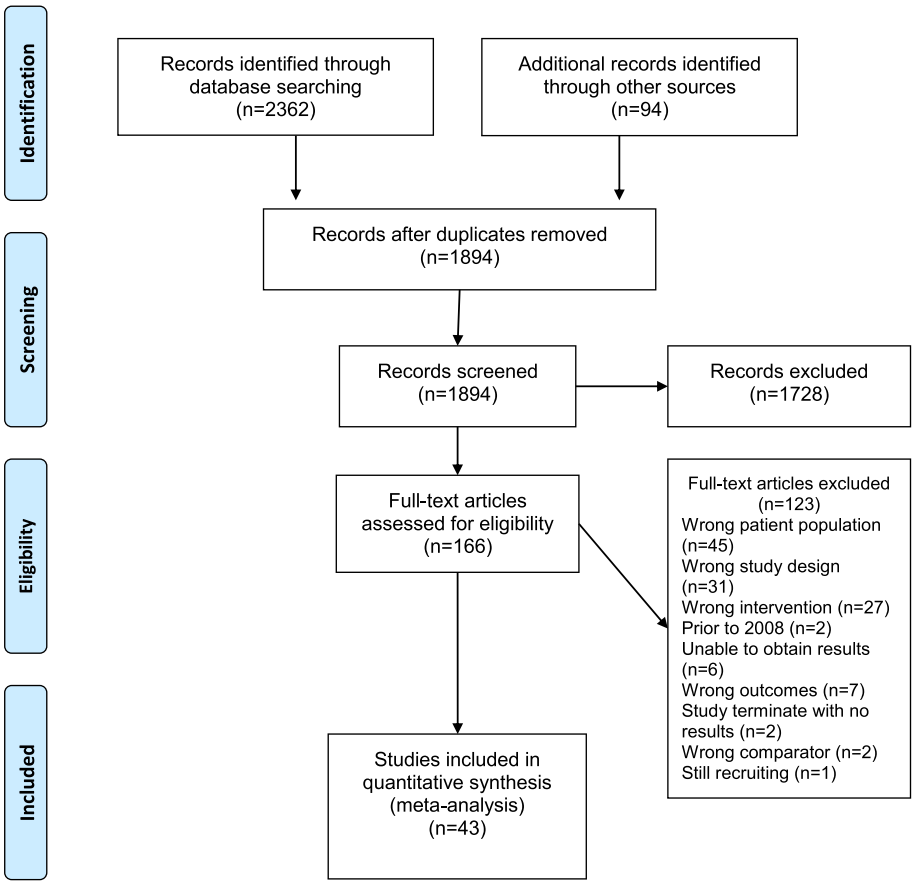

Fig. 1. PRISMA flow diagram of include studies in systematic review of medical abortion regimens at 12 weeks' gestation and above.

Table 1
Characteristics of included studies in systematic review and meta-analysis of medical abortion regimens at 12 weeks' gestation and above

Mifepristone–misoprostol vs. misoprostol only

Author, year, country	Participants (*N*)	Gestational age (weeks)	Intervention 1	Intervention 2
Akkenapally 2016 [25]	200	14–20	200 mg mifepristone oral 24 h→	600 mcg misoprostol vaginal loading dose→
India			600 mcg misoprostol vaginal loading dose→ 400 mcg misoprostol sublingual every 3 h up to 5 doses	400 mcg misoprostol sublingual every 3 h up to 5 doses
Dabash 2015 [26]	120	14–21	200 mg mifepristone oral 24 h→	Placebo 24 h→
Tunisia			400 mcg misoprostol buccal every 3 h up to 5 doses	400 mcg misoprostol buccal every 3 h up to 5 doses
Kapp 2007 [17]	64	18–23	200 mg mifepristone oral 24 h→	Placebo 24 h→
United States			400 mcg misoprostol buccal loading dose→ 200 mcg misoprostol buccal every 6 h	400 mcg misoprostol buccal loading dose→ 200 mcg misoprostol buccal every 6 h
Kulkarni 2014 [27]	60	13–20	200 mg mifepristone oral 48 h→	Placebo 48 h→
India			400 mcg misoprostol vaginal loading dose→ 200 mcg misoprostol vaginal every 6 h	400 mcg misoprostol vaginal loading dose→ 200 mcg misoprostol vaginal every 6 h
Mukhopadhyay 2012 [28]	122	12–20	200 mg mifepristone oral 48 h→	Placebo 48 h→
India			400 mcg misoprostol vaginal loading dose→ 200 mcg misoprostol vaginal every 4 h up to 5 doses	400 mcg misoprostol vaginal loading dose→ 200 mcg misoprostol vaginal every 4 h up to 5 doses
Nagaria 2011 [29]	200	12–28	200 mg mifepristone oral 12 h →	600 mcg misoprostol vaginal loading dose →
India			600 mcg misoprostol vaginal loading dose → 300 mcg misoprostol vaginal every 3 h up to 5 doses	300 mcg misoprostol vaginal every 3 h up to 5 doses
Ngoc 2011 [30]	260	14–21	200 mg mifepristone oral 24 h→	Placebo 24 h→
Vietnam			400 mcg misoprostol buccal every 3 h up to 5 doses	400 mcg misoprostol buccal every 3 h up to 5 doses

Mifepristone–misoprostol dosing regimens

Author, year, country	Participants	Gestational age (weeks)	Intervention 1	Intervention 2
Abbas 2016 [31]	509	12–22	200 mg mifepristone oral + 400 mcg misoprostol buccal (given simultaneously) → 400 mcg misoprostol buccal every 3 h	200 mg mifepristone oral 24 h→ 400 mcg misoprostol buccal every 3 h
Vietnam				
Naravage 2017 [15]	100	9–20	200 mg mifepristone oral 24 h→	200 mg mifepristone oral 48 h→
India, Sweden, Thailand, Vietnam			800 mcg misoprostol vaginal loading dose→ 400 mcg misoprostol sublingual every 3 h up to 4 doses	800 mcg misoprostol vaginal loading dose→ 400 mcg misoprostol sublingual every 3 h up to 4 doses
Chai 2009 [32]	141	12–20	200 mg mifepristone oral + 600 mcg misoprostol vaginal loading dose (given simultaneously) → 400 mcg misoprostol vaginal every 3 h up to 4 doses	200 mg mifepristone oral 36–38 h→ 600 mcg misoprostol vaginal loading dose→ 400 mcg misoprostol vaginal every 3 h up to 4 doses
Hong Kong, China				
Chaudhuri 2014 [33]	95	13–20	200 mg mifepristone oral 24 h→	200 mg mifepristone oral 48 h→
India			800 mcg misoprostol vaginal loading dose → 400 mcg misoprostol vaginal every 3 h for a maximum of 4 doses	800 mcg misoprostol vaginal loading dose → 400 mcg misoprostol vaginal every 3 h for a maximum of 4 doses
Chen 2013 [13]	1112	8–16	200 mg mifepristone oral 24 h→	200 mg mifepristone oral 24 h→
China			600 mcg misoprostol vaginal loading dose→ 600 mcg misoprostol oral every 3 h up to 4 doses	600 mcg misoprostol oral every 3 h up to 4 doses
			(3rd group) 100 mg mifepristone oral 24 & 48 h→ 600 mcg misoprostol vaginal every 12 h up to 3 doses	(4th group) 200 mg mifepristone oral 24 h→ 600 mcg misoprostol vaginal every 3 h up to 4 doses
Jinfeng 2015 [14]	327	8–16	100 mg mifepristone oral 24 & 48 h→	100 mg mifepristone oral 24 & 48 h→
China			400 mcg misoprostol oral every 3 h up to 4 doses	600 mcg vaginal misoprostol loading dose → 400 mcg misoprostol vaginal every 6 h, up to 4 doses

Hou 2010 [23] China	100	13–16	200 mg mifepristone oral 24 h→ 600 mcg misoprostol vaginal loading dose → 400 mcg misoprostol orally every 6 h up to 2 doses	200 mg mifepristone oral 48 h→ 600 mcg misoprostol vaginal loading dose → 400 mcg misoprostol orally every 6 h up to 2 doses
Mentula 2011 [24] Finland	227	13–24	200 mg mifepristone oral 24 h→ 400 mcg misoprostol vaginal every 3 h up to 5 doses	200 mg mifepristone oral 48 h→ 400 mcg misoprostol vaginal every 3 h up to 5 doses
Webster 1996 [34] United Kingdom	70	13–20	600 mg mifepristone oral 36–48 h→ 800 mcg misoprostol vaginal loading dose → 400 mcg misoprostol orally every 3 h up to 4 doses	200 mg mifepristone oral 36–48 h→ 800 mcg misoprostol vaginal loading dose → 400 mcg misoprostol orally every 3 h up to 4 doses

Mifepristone–misoprostol routes

Author, year, country	**Participants**	**Gestational age (weeks)**	**Intervention 1**	**Intervention 2**
Chen 2013 [13] China	556	8–16	200 mg mifepristone oral 24 h→ 600 mcg misoprostol oral every 3 h up to 4 doses	200 mg mifepristone oral 24 h→ 600 mcg misoprostol vaginal every 3 h up to 4 doses
Dabash 2017 [41] Tunisia, Armenia, Uzbekistan, Nepal	339	13–21	200 mg mifepristone oral 24 h→ 400 mcg misoprostol buccal every 3 h	200 mg mifepristone oral 24 h→ 400 mcg misoprostol sublingual every 3 h
Dickinson 2014 [20] Australia	302	14–22	200 mg mifepristone oral 24–48 h→ 800 mcg misoprostol vaginal loading dose → 400 mcg misoprostol vaginal every 4 h up to 5 doses	200 mg mifepristone oral 24–48 h→ 800 mcg misoprostol vaginal loading dose → 400 mcg misoprostol sublingual every 4 h up to 5 doses (3rd group) 200 mg mifepristone oral 24–48 h→ 800 mcg misoprostol vaginal loading dose → 400 mcg misoprostol oral every 4 h up to 5 doses
El-Refaey 1995 [35] United Kingdom	69	13–20	600 mg mifepristone oral 36–48 h→ 600 mcg misoprostol vaginal loading dose → 400 mcg misoprostol vaginal every 3 h	600 mg mifepristone oral 36–48 h→ 600 mcg misoprostol vaginal loading dose → 400 mcg misoprostol oral every 3 h
Garg 2015 [40] India	50	14–25	200 mg mifepristone oral 48 h→ 400 mcg misoprostol buccal loading dose → 200 mcg misoprostol buccal every 6 h up to 6 doses	200 mg mifepristone oral 48 h→ 200 mcg misoprostol vaginal every 6 h up to 6 doses
Hamoda 2005 [39] United Kingdom	76	13–20	200 mg mifepristone oral 36–48 h→ 600 mcg misoprostol sublingual loading dose → 400 mcg misoprostol sublingual every 3 h up to 5 doses	200 mg mifepristone oral 36–48 h→ 800 mcg misoprostol vaginal loading dose → 400 mcg misoprostol vaginal every 3 h up to 5 doses
Ho 1997 [36] Hong Kong, China	98	14–20	200 mg mifepristone oral 36–48 h→ 200 mcg misoprostol oral + placebo vaginal every 3 h up to 5 doses	200 mg mifepristone oral 36–48 h→ 200 mcg misoprostol vaginal + placebo oral every 3 h up to 5 doses
Ngai 2000 [37] Hong Kong, China	139	14–20	200 mg mifepristone oral 36–48 h→ 400 mcg misoprostol oral + placebo vaginal every 3 h up to 5 doses	200 mg mifepristone oral 36–48 h→ 200 mcg misoprostol vaginal + placebo oral every 3 h up to 5 doses
Tang 2005 [38] Hong Kong, China	118	12–20	200 mg mifepristone oral 36–48 h→ 400 mcg misoprostol oral+ placebo sublingual every 3 h up to 5 doses	200 mg mifepristone oral 36–48 h→ 400 mcg misoprostol sublingual + placebo oral every 3 h up to 5 doses

Misoprostol-only dosing regimens

Author, year, country	**Participants**	**Gestational age (weeks)**	**Intervention 1**	**Intervention 2**
Bhattacharjee 2012 [45] India	295	13–20	400 mcg misoprostol vaginal moistened with 5% acetic acid every 4 h up to 5 doses	400 mcg misoprostol vaginal dry every 4 h up to 5 doses
Carbonell 2008 [47] Cuba	210	12–20	600 mcg misoprostol vaginal every 6 h up to 4 doses	400 mcg misoprostol vaginal every 4 h up to 5 doses
Chaudhuri 2010 [44] India	185	12–20	400 mcg misoprostol vaginal every 6 h up to 4 doses	400 mcg misoprostol vaginal every 12 h up to 4 doses

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Dickinson 2003 [21] Australia	56	14–26	600 mcg misoprostol vaginal loading dose 6 h → 200 mcg misoprostol oral every 3 h	400 mcg misoprostol oral every 3 h
Herabutya 2005 [22] Thailand	279	14–26	600 mcg misoprostol vaginal every 6 h	600 mcg misoprostol vaginal every 12 h
Koh 2017 [42] Singapore	77	13–23	200 mcg misoprostol vaginal every 4 h up to 5 doses	400 mcg misoprostol vaginal every 4 h up to 5 doses
Ozerkan 2009 [48] Turkey	60	13–24	400 mcg misoprostol vaginal loading dose → 200 mcg misoprostol vaginal every 2 h up to 5 doses	600 mcg misoprostol vaginal loading dose → 400 mcg misoprostol vaginal every 4 h up to 2 doses
Pongsatha 2011 [46] Thailand	179	14–28	400 mcg misoprostol vaginal moistened with saline every 3 h	400 mcg misoprostol vaginal moistened with acetic acid every 3 h
Wong 2000 [43] Hong Kong, China	148	14–20	400 mcg misoprostol vaginal every 3 h up to 5 doses	400 mcg misoprostol vaginal every 6 h up to 3 doses

Misoprostol-only routes

Author, year, country	**Participants**	**Gestational age (weeks)**	**Intervention 1**	**Intervention 2**
Akoury 2004 [18] Canada	136	15–24	400 mcg misoprostol vaginal every 4 h up to 6 doses	400 mcg misoprostol oral every 4 h up to 6 doses
Al 2015 [54] Turkey	130	13–24	400 mcg misoprostol vaginal every 3 h up to 6 doses	400 mcg misoprostol buccal every 3 h up to 6 doses
Bhattacharjee 2008 [51] India	277	13–20	400 mcg misoprostol sublingual every 3 h up to 5 doses	400 mcg misoprostol vaginal every 3 h up to 5 doses
Desai 2016 [19] India	22	Mean 17.9 SD 2.4	600 mcg misoprostol vaginal	200 mcg misoprostol intracervical + 200 mcg misoprostol vaginal
Dickinson 2003 [21] Australia	57	14–26	400 mcg misoprostol vaginal every 6 h	400 mcg misoprostol oral every 3 h
Ellis 2010 [16] United States	64	17–23	400 mcg misoprostol buccal loading dose → 200 mcg misoprostol buccal every 5–6 h	400 mcg misoprostol vaginal loading dose → 200 mcg misoprostol vaginal every 5–6 h
Gilbert 2001 [49] New Zealand	54	Midtrimester[a]	400 mcg misoprostol vaginal loading dose 2 h → 200 mcg misoprostol vaginal every 4 h	400 mcg misoprostol vaginal loading dose 2 h → 200 mcg misoprostol oral every 4 h
Modak 2014 [52] India	134	13–20	400 mcg misoprostol sublingual every 3 h up to 5 doses	400 mcg misoprostol vaginal every 3 h up to 5 doses
Nautiyal 2014 [50] India	150	12–20	400 mcg misoprostol sublingual every 4 h up to 4 doses	400 mcg misoprostol vaginal every 4 h up to 4 doses (3rd group) 400 mcg misoprostol oral every 4 h up to 4 doses
Tang 2004 [55] Hong Kong, China	220	12–20	400 mcg misoprostol sublingual every 3 h up to 5 doses	400 mcg misoprostol vaginal every 3 h up to 5 doses
Von Hertzen 2009 [53] Armenia, Georgia, Hungary, India, Slovenia, South Africa, Vietnam	681	13–20	400 mcg misoprostol sublingual + placebo vaginal every 3 h up 5 doses	400 mcg misoprostol vaginal + placebo sublingual every 3 h up 5 doses

[a] Authors did not report the gestational age range.

400 mcg vaginally every 6 h (Supplements 6F and 7F) [15]. We analyzed 327 women in the 10- to 16-week subgroup. Group A experienced a higher rate of vomiting (RR 1.39, 95% CI 1.07–1.81, low certainty evidence). We found no differences in ongoing pregnancy rates.

3.3. Misoprostol routes in combination mifepristone–misoprostol regimens

Five trials with 1062 total subjects compared oral vs. vaginal routes of misoprostol (Fig. 5, Supplements 8A and 9A) [14,21,36–38]. Oral route resulted in higher rates of ongoing pregnancy at 24 h (RR 1.64, 95% CI 1.04–2.59, moderate certainty evidence), a lower rate of satisfaction (RR 0.88, 95% CI 0.80–0.97, moderate certainty evidence) and a higher rate of diarrhea (RR 1.51, 95% CI 1.07–2.13, low certainty evidence).

Two trials with 320 total subjects compared oral vs. sublingual routes of misoprostol (Fig. 6, Supplements 8B and 9B) [21,39]. The oral group had higher rates of ongoing pregnancy at 24 h (RR 2.17, 95% CI 1.02–4.64) and a longer median time to expulsion of pregnancy (1.9 h longer, range 1.72–2.08), both with low certainty evidence.

Two trials with 278 total subjects compared vaginal vs. sublingual routes of misoprostol (Fig. 7, Supplements 8C and 9C) [21,40]. One trial ($N = 50$) compared vaginal vs. buccal routes of misoprostol (Appendix 6D, Supplement 3D) [41]. Another trial ($N = 339$) compared

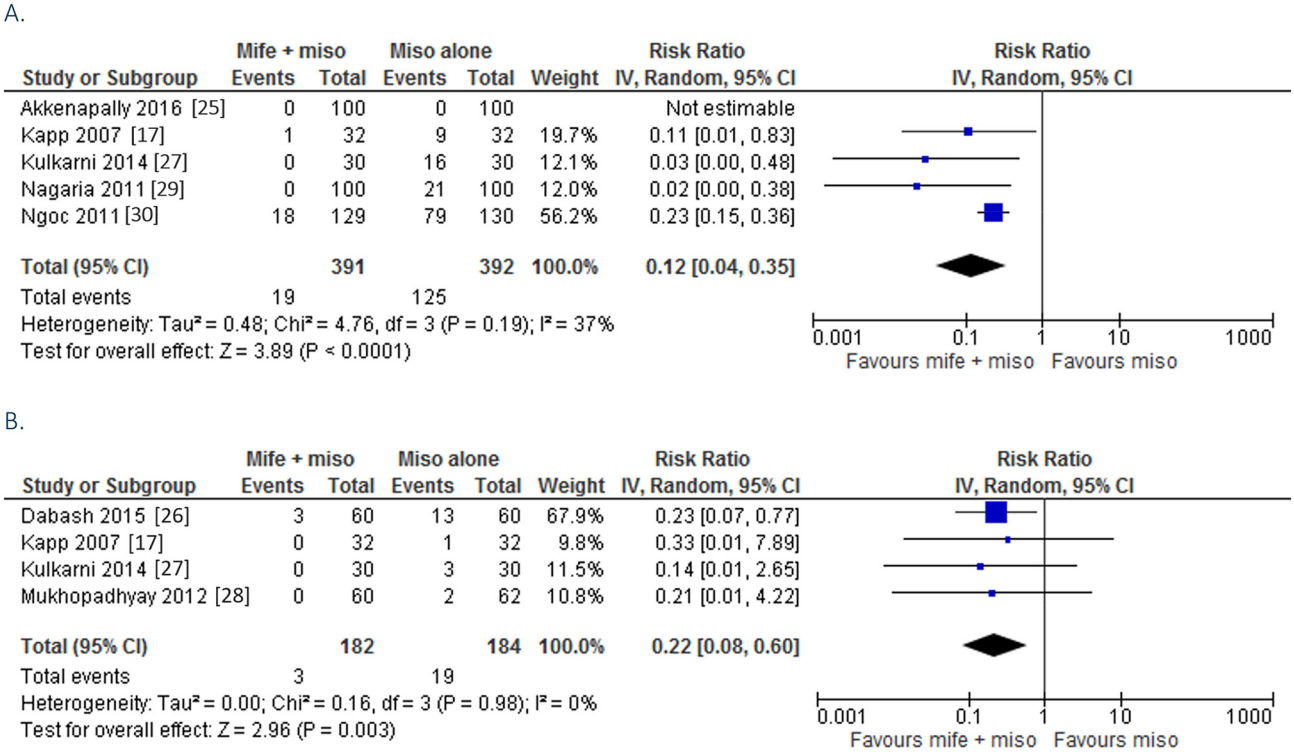


Fig. 2. Forest plots for mifepristone + misoprostol vs. misoprostol alone for medical abortion at 12 weeks' gestation and above (A) Ongoing pregnancy within 24 h (B) Ongoing pregnancy within 48 h.

sublingual vs. buccal routes of misoprostol (Appendix 6E, Supplement 3E) [42]. We found no differences in any outcomes across all comparisons.

3.4. Misoprostol-only dosing regimens

3.4.1. Misoprostol dosage

One trial with 77 subjects compared misoprostol 200 mcg vs. 400 mcg vaginally every 4 h (Supplements 10A and 11A) [43]. The 200-mcg group had a lower rate of complete abortion at 48 h (RR 0.76, 95% CI 0.61–0.95, at 48 h, low certainty evidence). We found no significant differences in ongoing pregnancy rates.

3.4.2. Misoprostol loading dose

One trial with 56 subjects evaluated a loading dose of misoprostol 600 mcg vaginally vs. no loading dose (Supplements 10B and 11B) [22]. The loading-dose group had a lower rate of ongoing pregnancy at 24 h (RR 0.47, 95% CI 0.23–0.96, very low certainty of evidence). The time to expulsion of pregnancy in the loading-dose group was a median of 25.5 h (95% CI 19.7–31.7) vs. 16.4 h (95% CI 13.5–23.8) (very low certainty evidence). Authors did not report SAEs.

3.4.3. Misoprostol dosing intervals

One trial with 148 subjects compared the use of misoprostol 400 mcg vaginally every 3 vs. 6 h (Supplements 10C and 11C) [44]. The 3-h dosing group had a lower rate of ongoing pregnancy at 48 h (RR 0.39, 95% CI

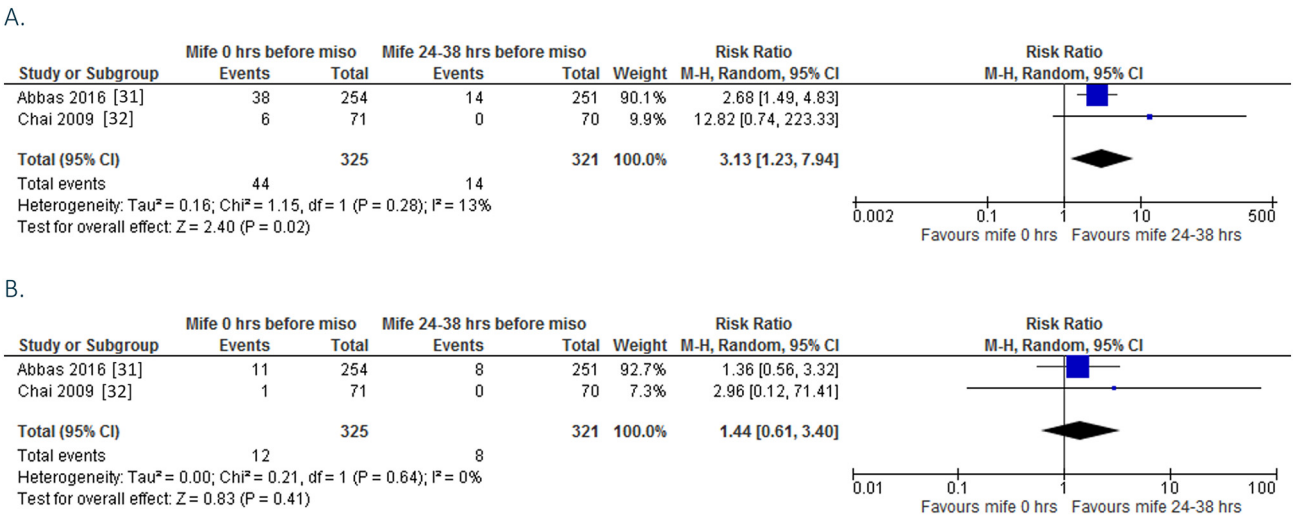


Fig. 3. Forest plots for simultaneous mifepristone + misoprostol vs. mifepristone given 24–38 h before misoprostol for medical abortion at 12 weeks' gestation and above. (A) Ongoing pregnancy within 24 h (B) Ongoing pregnancy within 48 h.

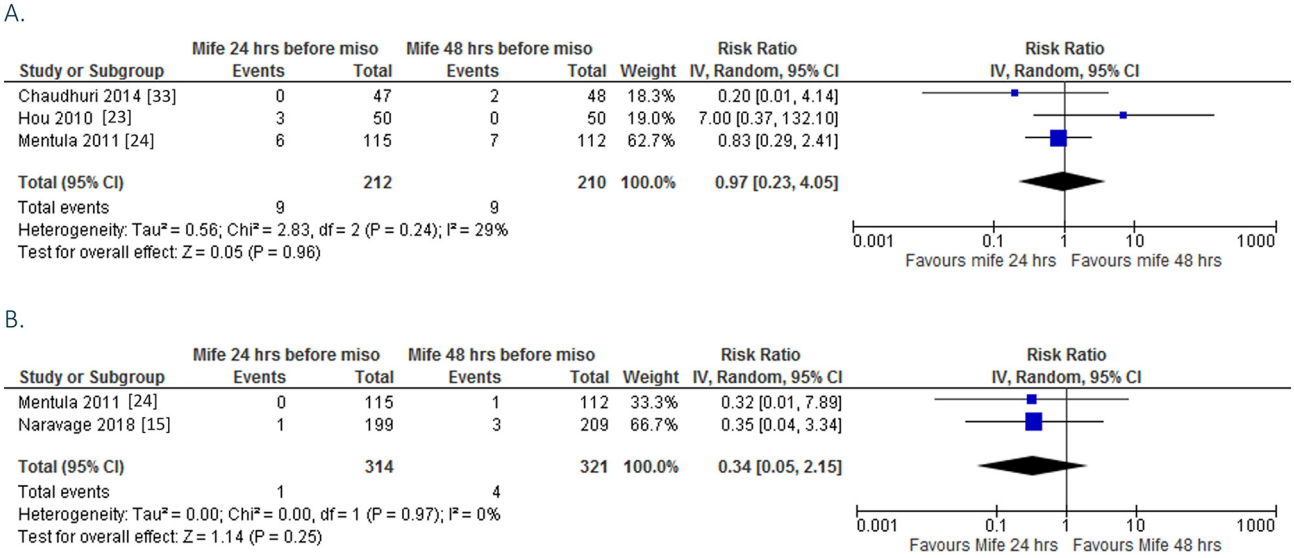


Fig. 4. Forest plots for mifepristone 24 h before misoprostol vs. mifepristone 48 h before misoprostol for medical abortion at 12 weeks' gestation or above. (A) Ongoing pregnancy within 24 h (B) Ongoing pregnancy within 48 h.

0.17–0.88, low certainty evidence). The 3-h dosing group also had a shorter mean time to expulsion of pregnancy by 19.2 h (range 2.38–36.02, moderate certainty). The authors did not report SAEs.

Two trials with 464 total subjects compared the use of misoprostol 400–600 mcg vaginally every 6 vs. 12 h (Fig. 8, Supplements 10D and 11D) [23,45]. The 6-h dosing group had higher rates of vomiting (RR 2.33, 95% CI 1.04–5.23, low certainty evidence). We found no differences in ongoing pregnancy rates.

3.4.4. Misoprostol preparation

Two trials with 474 total subjects compared the use of dry or saline-moistened vaginal misoprostol to acetic-acid-moistened vaginal misoprostol (Supplements 10E and 11E) [46,47]. We found no differences in any outcomes.

3.4.5. Variations in misoprostol-only regimens

Two trials with 270 total subjects compared a low-dose/high-frequency (400 mcg every 4 h) vs. high-dose/low-frequency (600 mcg every 6 h) misoprostol regimens (Supplements 10F and 11F) [48,49]. The low-dose/high-frequency group had a slightly longer mean time to expulsion of pregnancy by 2.8 h, SD 2.46 shorter to 8.06 longer (low certainty evidence). We found no differences in ongoing pregnancy rates.

3.5. Misoprostol routes in misoprostol-only regimens

Four trials with 347 total subjects compared oral to vaginal routes of misoprostol (Fig. 9, Supplements 12A and 13A) [19,22,50,51]. The oral group had higher ongoing pregnancy rates at 24 h (RR 3.60, 95% CI

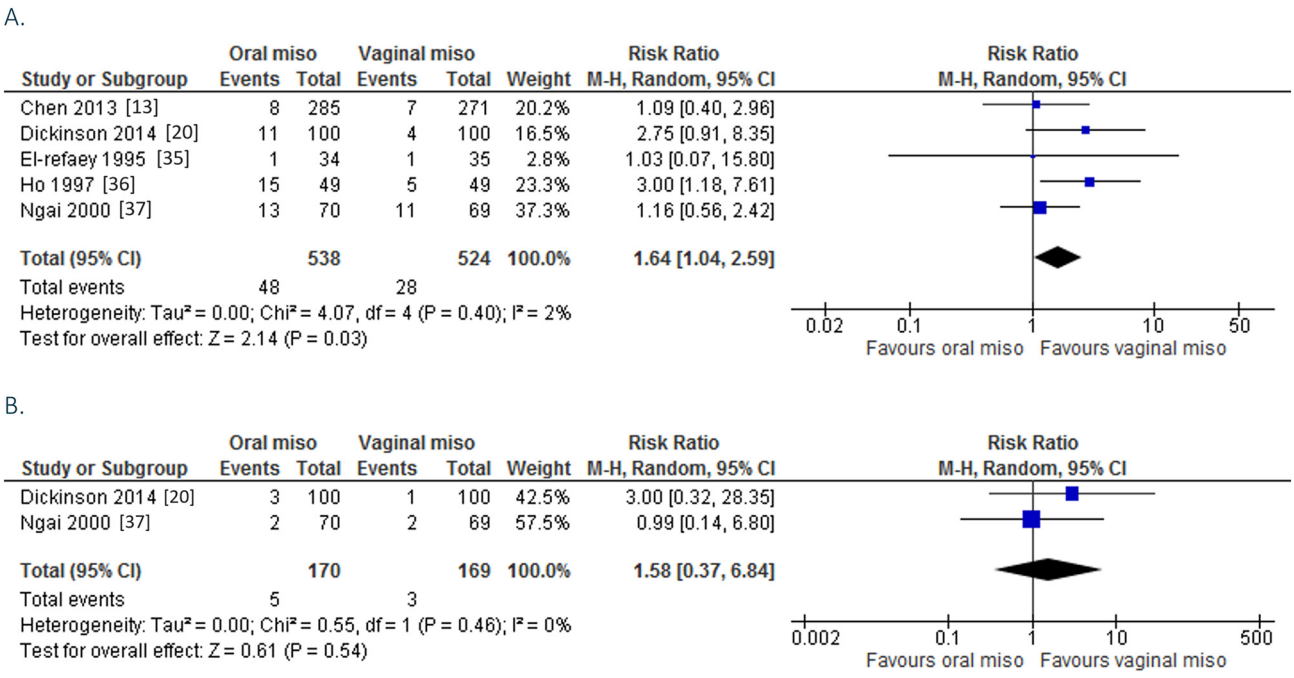


Fig. 5. Forest plots mifepristone plus oral vs. vaginal misoprostol for medical abortion at 12 weeks' gestation or above. (A) Ongoing pregnancy within 24 h (B) Ongoing pregnancy within 48 h.

Fig. 6. Forest plots for mifepristone plus oral vs. sublingual misoprostol for medical abortion at 12 weeks' gestation or above. Ongoing pregnancy within 24 h.

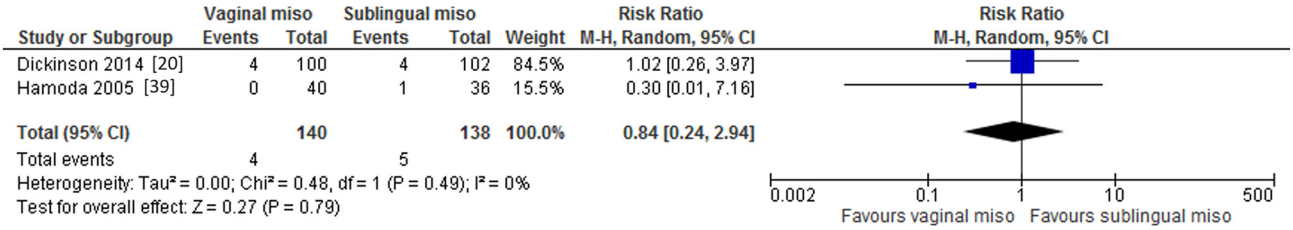


Fig. 7. Forest plots for mifepristone plus vaginal vs. sublingual misoprostol for medical abortion at 12 weeks' gestation or above. Ongoing pregnancy within 24 h.

1.99–6.51, moderate certainty evidence) and 48 h (RR 8.01, 95% CI 1.74–36.87, low certainty evidence). The oral group had a longer mean time to expulsion of pregnancy at 11.4 h longer, SD 9.81 to 12.47 longer (moderate certainty evidence). Rate of vomiting (RR 1.85, 95% CI 1.14–3.03, low certainty evidence) was higher in the oral than vaginal group.

One trial with 100 subjects compared oral to sublingual route of misoprostol (Supplements 12B and 13B) [51]. The oral group had a longer mean time to expulsion of pregnancy at 4.5 h longer (SD 14.3 h, range 7.5–19.4 vs. 9.8 h, range 4.5–17.9, low certainty evidence). The oral group also had less complete abortions (RR 0.63, 95% CI 0.46–0.88,

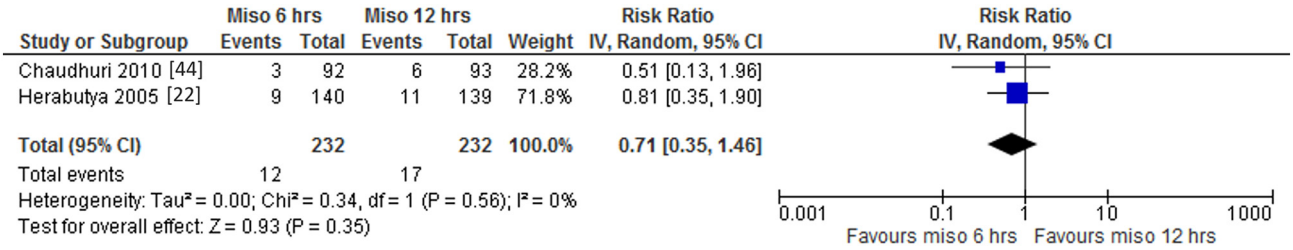
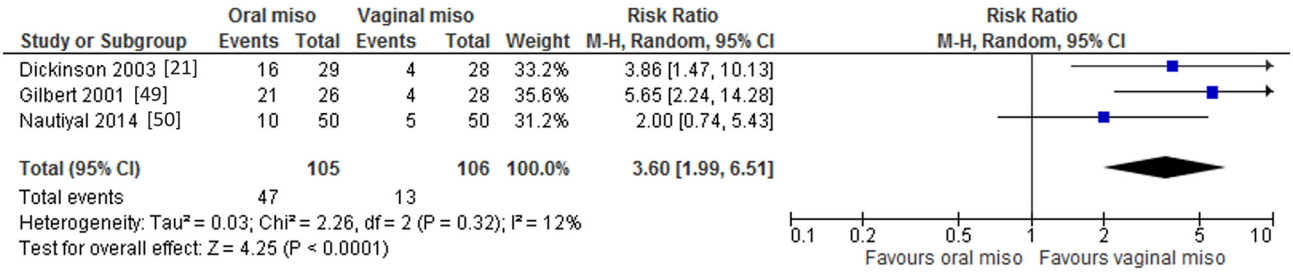


Fig. 8. Forest plots for misoprostol every 6 h vs. every 12 h for medical abortion at 12 weeks' gestation and above. Ongoing pregnancy within 48 h.

A.



B.

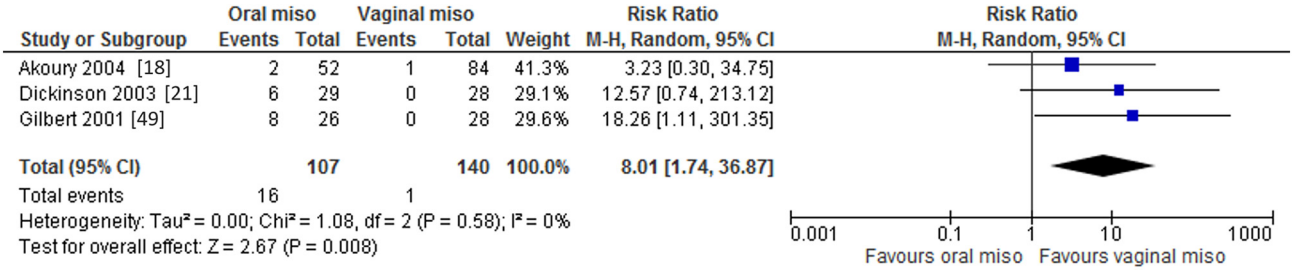


Fig. 9. Forest plots for oral vs. vaginal misoprostol for medical abortion at 12 weeks' gestation and above. (A) Ongoing pregnancy within 24 h (B) Ongoing pregnancy within 48 h.

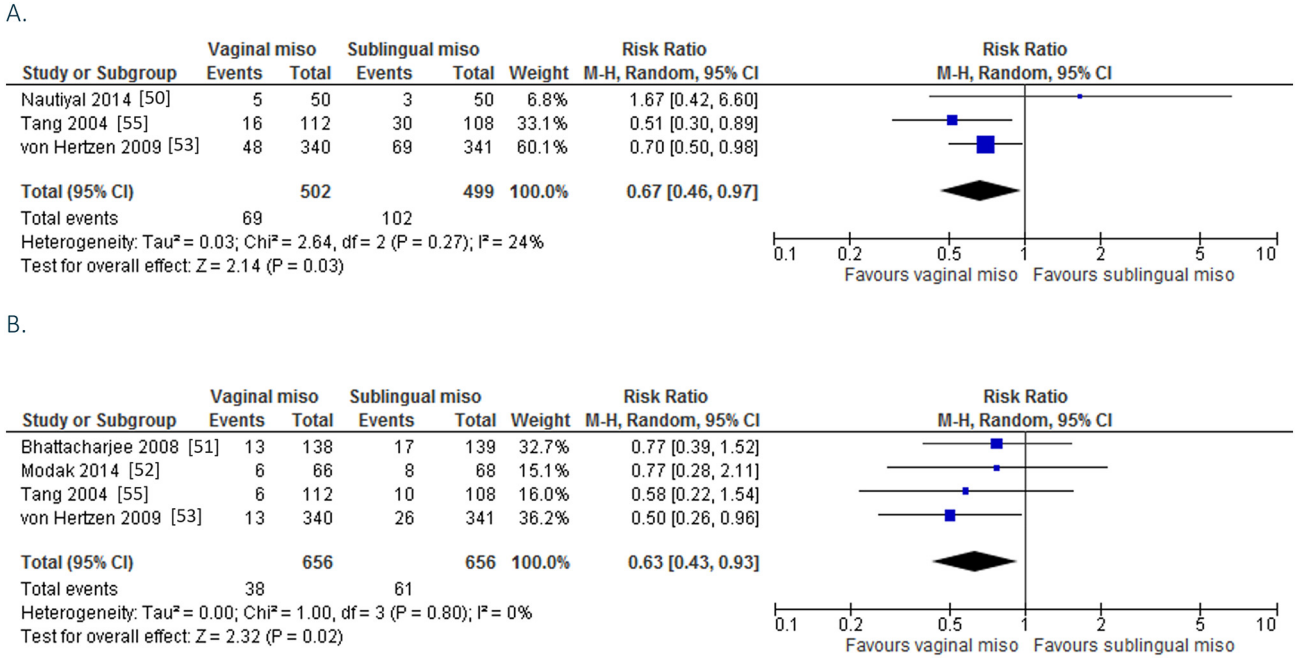


Fig. 10. Forest plots for vaginal vs. sublingual misoprostol for medical abortion at 12 weeks' gestation and above. (A) Ongoing pregnancy within 24 h (B) Ongoing pregnancy within 48 h.

very low certainty evidence). We found no differences in ongoing pregnancy rates.

Five trials with 1261 total subjects compared vaginal to sublingual route of misoprostol (Fig. 10, Supplements 12C and 13C) [39,51–54]. The vaginal group had lower rates of ongoing pregnancy at 24 (RR 0.67, 95% CI 0.46–0.97) and 48 h (RR 0.63, 95% CI 0.43–0.93 at 48 h), both with moderate certainty evidence. The vaginal group also had a lower rate of satisfaction (RR 0.42, 95% CI 0.25–0.71, moderate certainty evidence).

Two trials with 193 total subjects compared vaginal to buccal route of misoprostol (Supplements 12D and 13D) [17,55]. The vaginal group had lower ongoing pregnancy rates at 24, (RR 0.63, 95% CI 0.43–0.92) and at 48 h (RR 0.29, 95% CI 0.12–0.66), both with low certainty evidence.

One trial with 22 subjects compared vaginal to vaginal plus intracervical routes of misoprostol (Supplements 12E and 13E) [20]. The study reported no ongoing pregnancies or SAEs. We found no significant differences in any outcomes.

3.6. Serious adverse events

Across all included studies, authors reported 106 SAEs. Ten studies did not supply data on SAEs [22,26,27,30,31,41,44,49,54,56]. In removing the population of women from the 10 studies not reporting SAEs, we calculated an overall SAE rate of 1.7% (106/6313). A single trial reported a case of uterine rupture in a woman with one prior uterine incision (received regimen of mifepristone 200 mg 24–48 h before a loading dose of misoprostol 800 mcg vaginally and misoprostol 400 mcg vaginally every 4 h) [21].

In our analysis, we only critically appraised dichotomous data on the side effect of bleeding, often measured as hemorrhage (measured or estimated amount over a certain threshold) or excessive bleeding (as reported by the participant or provider). Sixteen studies also reported on continuous outcomes of bleeding, namely, the amount of blood loss or a change in hemoglobin [14,15,21,24,26,29,30,33,36,39,40,44,47–49,55]. Across all of these studies, there was no significant difference in bleeding among study arms from either a statistical or clinical standpoint.

4. Discussion

This systematic review and meta-analysis included 8284 women from 43 randomized clinical trials on management of second-trimester medical abortion. The WHO used the results of this review to directly inform its recent *Medical management of abortion* guidance [11]. Our review builds on the 2011 Cochrane review [5] of second-trimester medical abortion methods by evaluating 26 new trials [13–55]. Based on our analysis, we recommend a regimen of mifepristone 200 mg 1 to 2 days before misoprostol 400 mcg every 3 h via vaginal, sublingual or buccal routes. Our conclusions expanded upon those of the Cochrane review, which recommended mifepristone plus misoprostol vaginally every 3 h.

While our results suggest that a 1- to 2-day delay between mifepristone and misoprostol is more efficacious, closer spacing may be preferred by some women who wish to shorten the overall abortion process while accepting a slightly reduced efficacy and more side effects. Results of this review do not support the use of a misoprostol loading dose. While vaginal and sublingual routes have improved efficacy and side effect profiles over oral route, vaginal route additionally appears more efficacious than sublingual. Although data on the buccal route were limited in our review, buccal misoprostol is already used in many settings [57–59]. While pharmacokinetic studies have demonstrated that the shape of the buccal misoprostol absorption curve is similar to that of vaginal, buccal misoprostol has a lower area under the curve and serum levels [60,61]. Our analysis suggests that vaginal and buccal administrations have similar efficacy in combined mifepristone–misoprostol regimens and that buccal administration has decreased efficacy in misoprostol-only regimens. For those who prefer buccal administration, providers may counsel that data are limited and abortion success rates may be slightly lower than with vaginal route.

Our review includes a diverse population across all world regions and a range of income settings, making results more generalizable to a global population. We used a robust definition of SAEs, including need for hospitalization postabortion, blood transfusion, need for further surgery (beyond interventions to complete removal of products) or death, in an attempt to capture only the most objective and clinically significant safety outcomes. Our review reported an overall SAE rate of 1.7%, which is comparable to previously reported rates of 1%–2% [61–64].

Unlike the Wildschut review [4], which included studies with up to 20% fetal demise, we excluded trials with spontaneous fetal demise, making our results more generalizable to the induced medical abortion population.

Our population had a gestational age range of 12 to 28 weeks' gestation. Only a few studies provided outcome data stratified by gestational age subgroups; thus, we were unable to perform subanalyses for different gestational age groups or to assess outcomes prior to 24 weeks of gestation separately. Therefore, we are unable to draw any conclusions as to what regimens are ideal for specific gestational age ranges.

Out of the 8284 participants included in this review, 172 had a prior uterine incision with only one case of uterine rupture. We calculate a uterine rupture rate of 0.06% (1/172), which is lower than the 0.28% rate reported in a 2009 review on uterine rupture during second-trimester medical abortion by Goyal [65]. Goyal's review, however, did not include any randomized clinical trial data.

This analysis allowed us to identify gaps in the data on second-trimester medical abortion. Future studies should investigate the optimal dosing and frequency of misoprostol, particularly when combined with mifepristone. Direct comparisons of buccal misoprostol to sublingual or vaginal routes after mifepristone are lacking. Evidence from clinical trials on how to best manage women with prior uterine incisions is limited. We hope that continued rigorous research in the field of medical abortion will serve to further refine the regimens and best tailor them to women's needs.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conx.2020.100037.

Acknowledgments

The authors thank Sara De Masi for her contribution to data collection and Rucong Wu for his contribution to translation.

References

[1] Ganatra B, Gerdts C, Rossier C, et al. Global, regional, and subregional classification of abortions by safety, 2010–14: estimates from a Bayesian hierarchical model. Lancet. 2017;390:2372–81.
[2] Singh L SR, Sedgh G, Kwok L, Onda T. Abortion worldwide 2017: uneven progress and unequal access In: New York: Guttmacher Institute; 2018.
[3] World Health Organization. Safe abortion : technical and policy guidance for health systems. WHO; 2012 https://www.who.int/reproductivehealth/publications/unsafe_abortion/9789241548434/en/.
[4] Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. Cochrane Database Syst Rev. 2011;19(1):Cd005216.
[5] Veritas Health Innovation. Covidence systematic review software. In: Melbourne, Australia. Available at www.covidence.org.
[6] Higgins JPT, Green S, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions 6.o The Cochrane Collaboration ; 2019 www.training.cochrane.org/handbook.
[7] Review Manager (RevMan). Edited by The Nordic Cochrane Centre TCC. 5.3 ed. Copenhagen; 2014.
[8] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
[9] GRADEpro GDT: GRADEpro guideline development tool [software]. McMaster University; 2015 developed by Evidence Prime, Inc.). Available from gradepro.org.
[10] World Health Organization. Medical management of abortion. Geneva,Switzerland. Geneva: WHO; 2018 https://www.who.int/reproductivehealth/publications/medical-management-abortion/en/.
[11] World Health Organization. Handbook for guideline development Geneva, Switzerland WHO 2nd ed. https://apps.who.int/iris/handle/10665/145714.
[12] World Bank. World Bank list of economies. World Bank; June 2018 https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.
[13] Chen QJ, Zhang J, Huang ZR, 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;24:101–13.
[14] Jinfeng Q, Xiaoping J, Shuying W, et al. Efficacy and safety of mifepristone combined with misoprostol for termination of pregnancy; between 8 and 16 weeks of gestation. Zhonghua Fu Chan Ke Za Zhi. 2015:505–9.
[15] Naravage W, Vemer H. Personal communication: Mifepristone and misoprostol for the termination of pregnancy at 64–140 days since LMP Unpublished results ; 2018 Contact author at: wanapa_naravage@yahoo.com.
[16] Ellis SC, Kapp N, Vragpvoc O, Borgata L. Randomized trial of buccal versus vaginal misoprostol for induction of second trimester abortion. Contraception. 2010;81:441–5.
[17] Kapp N, Borgatta L, Stubblefield P, Vragovic O, Moreno N. Mifepristone in second-trimester medical abortion: a randomized controlled trial. Obstet Gynecol. 2007;110:1304–10.
[18] Akoury HA, Hannah ME, Chitayat D, Thomas M, Winsor E, Ferris LE, et al. Randomized controlled trial of misoprostol for second-trimester pregnancy termination associated with fetal malformation. Am J Obstet Gynecol. 2004;190:755–62.
[19] Desai G, Chandavarkar A, Gopal S, Sawant G, Desai S. Second trimester medical termination of pregnancy with combined intracervical and intravaginal misoprostol: comparative analysis with intravaginal misoprostol — a pilot study. J Obstet Gynaecol India. 2016:157–60.
[20] Dickinson J, Jennings B, Doherty D. Mifepristone and oral, vaginal, or sublingual misoprostol for second-trimester abortion: a randomized controlled trial. Obstet Gynecol. 2014;123:1162–8.
[21] Dickinson JE, Evans SF. A comparison of oral misoprostol with vaginal misoprostol administration in second-trimester pregnancy termination for fetal abnormality. Obstet Gynecol. 2003;101:1294–9.
[22] Herabutya Y, Chanrachakul B, Punyavachira P. A randomised controlled trial of 6 and 12 hourly administration of vaginal misoprostol for second trimester pregnancy termination. BJOG. 2005;112:1297–301.
[23] Hou S, Zhang L, Chen Q, Fang A, Cheng L. One- and two-day mifepristone-misoprostol intervals for second trimester termination of pregnancy between 13 and 16 weeks of gestation. Int J Gynecol Obstet. 2010:126–30.
[24] Mentula M, Suhonen S, Heikinheimo O. One- and two-day dosing intervals between mifepristone and misoprostol in second trimester medical termination of pregnancy — a randomized trial. Hum Reprod. 2011:2690–7.
[25] Akkenapally PL. A comparative study of misoprostol only and mifepristone plus misoprostol in second trimester termination of pregnancy. J Obstet Gynaecol India. 2016;66:251–7.
[26] Dabash R, Chelli H, Hajri S, Shochet T, Raghavan S, Winikoff B. A double-blind randomized controlled trial of mifepristone or placebo before buccal misoprostol for abortion at 14–21 weeks of pregnancy. Int J Gynecol Obstet. 2015:40–4.
[27] Kulkarni K. Pre-induction with mifepristone for second trimester termination of pregnancy. J Obstet Gynaecol India. 2014:102–4.
[28] Mukhopadhyay P, Bag T, Kyal A, Bhuniya A, Saha T. Second trimester abortion with vaginal misoprostol: is there any advantage with prior mifepristone priming? A comparative study. South Asian Federation of Obstetrics and Gynaecology. 2012:25–7.
[29] Nagaria TN. Misoprostol vs mifepristone and misoprostol in second trimester termination of pregnancy. J Obstet Gynaecol India. 2011:659–62.
[30] Ngoc NTN, Shochet T, Raghavan S, Blum J, Nga NT, Minh NT, et al. Mifepristone and misoprostol compared with misoprostol alone for second-trimester abortion: a randomized controlled trial. Obstet Gynecol. 2011;118:601–8.
[31] Abbas DF, Blum J, Ngoc NTN, Nga NT, Chi HT, Martin R, et al. Simultaneous administration compared with a 24-hour mifepristone-misoprostol interval in second-trimester abortion. Obstet Gynecology. 2016;128:1077–83.
[32] Chai J, Tang O, Hong Q, Chen QF, Cheng LN, Ng E, et al. A randomized trial to compare two dosing intervals of misoprostol following mifepristone administration in second trimester medical abortion. Human Reprod. 2009:320–4.
[33] Chaudhuri P, Mandal A, Das C, Mazumdar A. Dosing interval of 24 hours versus 48 hours between mifepristone and misoprostol administration for mid-trimester termination of pregnancy. Obstet Gynecol Int J. 2014:134–8.
[34] Webster D, Penney GC, Templeton A. A comparison of 600 and 200 mg mifepristone prior to second trimester abortion with the prostaglandin misoprostol. Br J Obstet Gynaecol. 1996;103:706–9.
[35] el-Refaey H, Templeton A. Induction of abortion in the second trimester by a combination of misoprostol and mifepristone: a randomized comparison between two misoprostol regimens. Hum Reprod. 1995;10:475–8.
[36] Ho PC, Ngai SW, Liu KL, Wong GC, Lee SW. Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy. Obstet Gynecol. 1997;90:735–8.
[37] Ngai SW, Tang OS, Ho PC. Randomized comparison of vaginal (200 microg every 3 h) and oral (400 microg every 3 h) misoprostol when combined with mifepristone in termination of second trimester pregnancy. Hum Reprod. 2000;15:2205–8.
[38] Tang OS, Chan CC, Kan AS, Ho PC. A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12–20 weeks gestation. Hum Reprod. 2005;20:3062–6.
[39] Hamoda H, Ashok PW, Flett GM, Templeton A. A randomized trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion at 13–20 weeks gestation. Hum Reprod. 2005;20:2348–54.
[40] Garg G, Takkar N, Sehgal A. Buccal versus vaginal misoprostol administration for the induction of first and second trimester abortions. J Obstet Gynaecol India. 2015:111–6.
[41] Dabash R, Chong E, Bracken H, Tsereteli T, Abrahamyan R, Hajri S, et al. A randomized controlled trial comparing repeat doses of 400 mcg sublingual to buccal misoprostol after mifepristone for termination of pregnancy 13–21 weeks. Contraception. 2017;95:515.
[42] Koh DSC, Ang EPJ, Coyuco JC, Teo HZ, Huang X, Wei X, et al. Comparing two regimens of intravaginal misoprostol with intravaginal gemeprost for second-trimester pregnancy termination: a randomised controlled trial. J Fam Plann Reprod Health Care. 2017;43:252–9.
[43] Wong KS, Ngai CS, Yeo EL, Tang LC, Ho PC. A comparison of two regimens of intravaginal misoprostol for termination of second trimester pregnancy: a randomized comparative trial. Hum Reprod. 2000;15:709–12.

[44] Chaudhuri S, Banerjee P, Mundle M, Mitra S. A comparison of two regimens of misoprostol for second trimester medical termination of pregnancy: a randomized trial. Trop Doct. 2010:144–8.
[45] Bhattacharjee N, Saha S, Ganguly R, et al. A randomized comparative study on vaginal administration of acetic acid-moistened versus dry misoprostol for mid-trimester pregnancy termination. Arch Gynecol Obstet. 2012:311–6.
[46] Pongsatha S, Tongsong T. Randomized controlled study comparing misoprostol moistened with normal saline and with acetic acid for second-trimester pregnancy termination. Is it different? J Obstet Gynaecol Res. 2011:882–6.
[47] Carbonell JL, Torres MA, Reyes R, Ortega L, García-Gallego F, Sánchez C. Second-trimester pregnancy termination with 600-μg vs. 400-μg vaginal misoprostol and systematic curettage postexpulsion: a randomized trial. Contraception. 2008;77:50–5.
[48] Ozerkan K, Ocakoglu G, Rehimli S, Uncu G, Develioglu O. A comparison of low-dose and high-dose protocols of vaginal misoprostol for second trimester termination of pregnancy. Clin Exp Obstet Gynecol. 2009;36:245–7.
[49] Gilbert A, Reid R. A randomised trial of oral versus vaginal administration of misoprostol for the purpose of mid-trimester termination of pregnancy. Aust N Z J Obstet Gynaecol. 2001;41:407–10.
[50] Nautiyal D, Mukherjee K, Perhar I, Banerjee N. Comparative study of misoprostol in first and second trimester abortions by oral, sublingual, and vaginal routes. J Obstet Gynaecol India. 2014;65:1–5.
[51] Bhattacharjee N, Saha SP, Ghoshroy SC, Bhowmik S, Barui G. A randomised comparative study on sublingual versus vaginal administration of misoprostol for termination of pregnancy between 13 to 20 weeks. Aust N Z J Obstet Gynaecol. 2008;48:165–71.
[52] Modak R, Biswas D, Ghosh A, Pal A, Mandal T. Comparative study of sublingual and vaginal misoprostol in second trimester induced abortion. Open J Obstet Gynecol. 2014;4:751–6.
[53] Von Hertzen H, Piaggio G, Wojdyla D, Nguyen TM, Marions L, Okoev G, et al. Comparison of vaginal and sublingual misoprostol for second trimester abortion: randomized controlled equivalence trial. Human Reprod. 2009;24:106–12.
[54] Al R, Yapca O. Vaginal misoprostol compared with buccal misoprostol for termination of second-trimester pregnancy: a randomized controlled trial. Obstet Gynecol. 2015;126:593–8.
[55] Tang OS, Lau WN, Chan CC, Ho PC. A prospective randomised comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. BJOG. 2004;111:1001–5.
[56] practice bulletin no ACOG. 135: second-trimester abortion. Obstet Gynecol. 2013;121:1394–406.
[57] Ipas. Clinical updates in reproductive health. NC: Chapel Hill; 2018.
[58] Louie KS, Chong E, Tsereteli T, Avagyan G, Abrahamyan R, Winikoff B. Second trimester medical abortion with mifepristone followed by unlimited dosing of buccal misoprostol in Armenia. Eur J Contracept Reprod Health Care. 2017;22:76–80.
[59] Meckstroth KR, Whitaker AK, Bertisch S, Goldberg AB, Darney PD. Misoprostol administered by epithelial routes: drug absorption and uterine response. Obstet Gynecol. 2006;108:582–90.
[60] Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. Int J Gynaecol Obstet. 2007;99:S160–7.
[61] Autry AM, Hayes EC, Jacobson GF, Kirby RS. A comparison of medical induction and dilation and evacuation for second-trimester abortion. Am J Obstet Gynecol. 2002;187:393–7.
[62] Bryant AG, Grimes DA, Garrett JM, Stuart GS. Second-trimester abortion for fetal anomalies or fetal death: labor induction compared with dilation and evacuation. Obstet Gynecol. 2011;117:788–92.
[63] Grossman D, Constant D, Lince N, Alblas M, Blanchard K, Harries J. Surgical and medical second trimester abortion in South Africa: a cross-sectional study. BMC Health Serv Res. 2011;11:224.
[64] Whitley KA, Trinchere K, Prutsman W, Quinones JN, Rochon ML. Midtrimester dilation and evacuation versus prostaglandin induction: a comparison of composite outcomes. Am J Obstet Gynecol. 2011;205:386 e381 7.
[65] Goyal V. Uterine rupture in second-trimester misoprostol-induced abortion after cesarean delivery: a systematic review. Obstet Gynecol. 2009;113:1117–23.