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Review article

First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review☆

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Abstract

Background: The dose of mifepristone approved by most government agencies for medical abortion is 600 mg. Our aim was to summarize extant data on the effectiveness and safety of regimens using the widely recommended lower mifepristone dose, 200 mg, followed by misoprostol in early pregnancy and to explore potential correlates of abortion failure.

Study Design: To identify eligible reports, we searched Medline, reviewed reference lists of published reports, and contacted experts to identify all prospective trials of any design of medical abortion using 200 mg mifepristone followed by misoprostol in women with viable pregnancies up to 63 days' gestation. Two authors independently extracted data from each study. We used logistic regression models to explore associations between 15 characteristics of the trial groups and, separately, the rates of medical abortion failure and of ongoing pregnancy.

Results: We identified 87 trials that collectively included 120 groups of women treated with a regimen of interest. Of the 47,283 treated subjects in these groups, abortion outcome data were reported for 45,528 (96%). Treatment failure occurred in 2,192 (4.8%) of these evaluable subjects. Ongoing pregnancy was reported in 1.1% (499/45,150) of the evaluable subjects in the 117 trial groups reporting this outcome. The risk of medical abortion failure was higher among trial groups in which at least 25% of subjects had gestational age >8 weeks, the specified interval between mifepristone and misoprostol was less than 24 h, the total misoprostol dose was 400 mcg (rather than higher), or the misoprostol was administered by the oral route (rather than by vaginal, buccal, or sublingual routes). Across all trials, 119 evaluable subjects (0.3%) were hospitalized, and 45 (0.1%) received blood transfusions.

Conclusions: Early medical abortion with mifepristone 200 mg followed by misoprostol is highly effective and safe.

Keywords: Medical abortion; Mifepristone; Misoprostol; Systematic review

1. Introduction

Since mifepristone was introduced in France and China more than two decades ago, medical abortion with this antiprogestin has expanded rapidly throughout the world. Mifepristone is now registered in 50 countries (www.gynuity.org, accessed 14 December 2011). In the United States, about one fifth of all outpatient abortions are performed medically [1], and in several countries in Europe, the proportion exceeds 60% [2,3].

Although medical abortion regimens approved by most government regulatory agencies specify 600 mg mifepristone, in practice, a dose of 200 mg is standard worldwide [4–7]. A prostaglandin, misoprostol, is administered after the mifepristone to enhance success. The dose, route, and timing of administration of misoprostol are not standardized. In the United States, affiliates of Planned Parenthood Federation of America provide 800 mcg buccally 24–48 h after the mifepristone [4]. The International Federation of Obstetricians and Gynaecologists recommends either vaginal, buccal, or sublingual administration [5] as do the World Health Organization [6] and the United Kingdom Royal College of Obstetricians and Gynaecologists [7], which also recommend

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oral dosing at gestational ages up to 49 days. Lower doses, divided doses, oral administration, and a shorter or longer interval between the two drugs also have been used clinically or evaluated in research studies.

The purpose of this review is to summarize published data on the effectiveness and safety of regimens including 200 mg mifepristone followed by misoprostol for early medical abortion. We also explore whether variation among studies in the frequency of medical abortion failure could be explained by characteristics of the study designs, treatment protocols, or study populations.

2. Materials and methods

We searched Medline using PubMed on 7 July 2011 for studies of medical abortion using mifepristone and misoprostol. Our search strategy was as follows: (abortion OR pregnancy termination OR termination of pregnancy) AND (mifepristone OR RU 486 OR RU-486 OR RU486 OR Mifegyne OR Mifeprex OR Medabon) AND (misoprostol OR prostaglandin). In addition, we reviewed the reference lists of relevant articles, and we contacted experts in the field for information about any published or unpublished trials not discovered in our search.

Two authors (E.G.R., C.S.) independently examined the search results (titles and as necessary abstracts and full publications) and other available information to identify all English language reports of prospective trials that included at least one group of women with viable first trimester pregnancies who were treated with a specified abortion regimen consisting of 200 mg mifepristone followed by misoprostol. These trials included randomized trials, cohort studies, and case series studies. For each group of interest in these reports, the same two authors separately abstracted data, including information about the study design and treatment protocol, the number and characteristics of women treated, and the numbers who had medical abortion failure, medical abortion failure with a diagnosed ongoing (viable) pregnancy, hospitalization, and blood transfusion. We contacted some authors to obtain additional data or to clarify details about the studies. We resolved discrepancies by discussion.

In some reports, the effectiveness analyses excluded subjects who initiated treatment but failed to complete the full prescribed medical abortion regimen. Our analyses included all pregnant women in each trial group who received at least mifepristone and who had a gestational age of 63 days or less, were not known to have an ectopic pregnancy, and had a reported abortion outcome. Most trials defined medical abortion failure as need for surgical intervention to complete the abortion, but a few used other definitions, such as failure to abort within 24 h after the misoprostol [8] and use of additional abortifacient drugs after the initially prescribed regimen [9]. Of necessity, we used the authors' definitions, but when possible, we also included as failures ongoing pregnancies that were continued at the patient's choice after ingestion of mifepristone.

In abstracting data about protocols and study populations, we combined the original authors' categories that were similar but not necessarily identical; for example, in recording gestational age ranges, we considered "<63 days", "≤63 days", "<9 weeks", and "≤9 weeks" all to be equivalent, and we considered subjects who had had no live births to be nulliparous if the report did not describe parity (including both live births and stillbirths). In recording parity and the gestational age distribution, we accepted figures for either the entire enrolled trial population or the analyzed population, as provided by the authors. We used our judgment to resolve internal inconsistencies and to correct frank errors noted in a few reports.

Our analysis considered each group from each trial (regardless of study design) as a separate case-series. We combined data across trial groups to calculate the proportion of subjects who had medical abortion failure and the proportion who had ongoing pregnancy. We used exact Pearson chi-square goodness-of-fit tests, calculated using StatXact, Version 8.0 (Cytel Inc., Cambridge, MA, USA), to assess heterogeneity across trial groups in both outcomes. To explore possible explanations for heterogeneity, we used logistic regression to examine associations between selected characteristics of the trial groups and, separately, medical abortion failure rate and ongoing pregnancy rate. The models controlled for nesting of groups within trial using generalized estimating equations with an independence working correlation matrix. The response for the models was the ratio of the number of events to the number of evaluable patients for each trial group (conducted in SAS, version 9.2, SAS Institute, Cary NC, USA); thus, model results were weighted by trial group sample size. We used "missing" categories to include trial groups with missing predictor data wherever relevant. The models included interaction terms for misoprostol dose and route of first dose. We excluded from both models one trial group of 4 women treated with 200 mcg misoprostol [10]. We excluded from the ongoing pregnancy model 3 trial groups in which ongoing pregnancy was not assessed [11–13], and to allow model convergence, we also excluded 4 groups in which women received misoprostol 600 mcg sublingual [14–17] because no ongoing pregnancies occurred in any groups with that dose/route combination. For one study in which the misoprostol dose was increased from 400 to 800 mcg partway through [18], we estimated the number of women and events in each of the two respective trial groups by assuming that the enrollment rate was constant over the course of the study. In reviewing the results, we focused on associations that were both substantial (odds ratio >1.5 or <0.67) and significant ($p<.05$).

A previously published protocol for this systematic review does not exist.

3. Results

The Medline search yielded 860 citations. Of these, 81 included at least one group of women who were treated with an abortion regimen that used 200 mg mifepristone followed by misoprostol in viable first trimester pregnancy [8–88]. In addition, we became aware of six reports of unpublished trials (M. Pena and S. Raghavan, Gynuity Health Projects, personal communication) that met these criteria.

The 87 trials included 36 randomized trials and 51 prospective cohort or case series studies conducted at 314 sites in 35 countries (Table 1). Sixty-three of the trials were performed between 1994 and 2011; the other 24 reports did not provide dates of data collection. Inclusion criteria for the trials were similar and broad: in general, any woman who requested medical abortion, did not have contraindications to the abortion drugs, and was within a specified gestational age range (determined by ultrasound or clinically) was eligible. Some trials had age restrictions and/or excluded women with multiple gestations.

The 87 trials included 120 groups of women treated with a regimen of interest: 62 trials studied a single such regimen, 18 studied two, six studied three, and one studied four (Appendix). The total prescribed dose of misoprostol in the regimens studied varied from 200–6400 mcg. In most trial groups, the misoprostol was delivered in one administration, but 13 groups received the total dose in divided increments over 1–7 days. Routes of administration included vaginal, oral, buccal and sublingual. The two most commonly studied regimens used 800 mcg misoprostol vaginally or 400 mcg orally. The interval between the mifepristone and the misoprostol ranged from 0 to 72 h. Some protocols required that all subjects receive the misoprostol in the clinic, whereas others allowed most or all women to take the misoprostol at home. In nearly half the groups, the treatment protocol specified that selected subjects who did not abort after the initial treatment should be offered one or more additional doses of misoprostol rather than immediate surgical evacuation.

The timing of the initial follow-up evaluation of abortion success varied from 1–21 days after mifepristone administration. In about half the trial groups, ultrasound was used routinely at the follow-up visit to determine whether the medical abortion regimen resulted in complete abortion and, if not, whether the pregnancy was ongoing. In other groups, outcome assessment, including the diagnosis of ongoing pregnancy, relied primarily or solely on patient symptoms and/or clinical examination. Some trials allowed collection of outcome information by telephone or by review of outside records. No trial had explicit criteria for hospitalization and transfusion of subjects.

The 120 trial groups included a total of 47,283 treated subjects, of whom 45,528 (96%) provided evaluable data for our effectiveness analyses (Table 1). The median proportion of treated subjects with missing outcome data was 1.3% (range 0–19%). The number of evaluable subjects in the 120 groups ranged from 4 to 4,132.

Among all evaluable subjects, 2,192 (4.8%) had medical abortion failure (Table 2). Across trial groups, the proportion with this outcome ranged from 0 to 40% (Fig. 1A). Half the groups had failure rates of 4.8% or less, and more than 90% of the evaluable subjects were in trial groups in which the failure proportion was 8.8% or less.

In 84 trials (117 groups), researchers noted whether or not each patient with medical abortion failure was diagnosed with ongoing pregnancy at the time of the failure ascertainment (Table 2). Of the 45,150 evaluable subjects in these trials, 499 (1.1%) had ongoing pregnancies. Across these groups, the median percentage of subjects with ongoing pregnancies was 0.7%, and 90% of the subjects were in groups in which less than 2.9% of subjects had ongoing pregnancy (Fig. 1B). The 499 ongoing pregnancies constituted 23% of the 1,976 medical abortion failures in these groups.

We found strong evidence of heterogeneity across trial groups in both the proportion of subjects who had medical abortion failure and the proportion who had ongoing pregnancy ($p<.001$ for both outcomes). Logistic regression models included as independent variables all the characteristics listed in Table 2. These models found few associations that were both substantial and significant. After adjustment for other characteristics included in the model, groups in which at least 25% of the women were in the ninth week of pregnancy had higher medical abortion failure rates than groups in which fewer women were so advanced in gestation (OR 1.5; 95% CI 1.1–2.0). Groups instructed to take the misoprostol <23 h after the mifepristone also had higher medical abortion failure rates than other groups (OR 2.1; 95% CI 1.4–3.2). At each total misoprostol dose level, oral administration was associated with higher medical abortion failure rates than each of the other three routes, but no substantial differences were noted among the other routes. Similarly, for each route, 400 mcg misoprostol was associated with higher failure rates than higher doses, although not all of these associations were significant.

Associations of misoprostol dose and route with ongoing pregnancy were mostly consistent with the associations with failure of all types; that is, both the oral route and the 400 mcg dose of misoprostol were generally associated with higher ongoing pregnancy rates than other doses and other routes. Ongoing pregnancy was twice as common in groups in which ultrasound was not routinely used to confirm success than in groups in which it was used in all women (OR 2.0, 95% CI 1.0–3.9). No notable associations were apparent between ongoing pregnancy rates and of any of the other group characteristics, however.

Across all trials, 119 of 45,528 evaluable subjects (0.3%) were hospitalized; of these, 46 hospitalizations (38%) occurred in a single trial [21] which included 4,132 treated women. Most of the hospitalizations were for vaginal bleeding, pelvic pain, or infection; some were for ectopic

Table 1
Characteristics of trial groups, subjects, medical abortion failures and ongoing pregnancies

	Trial groups[a]	Evaluable subjects[a]	Abortion failure		Ongoing pregnancy	
	N=120 (117)	N=45,528 (45,150)	N=2,192		N=499	
	n	*n*	*n*	%[b]	*n*	%[b]
Study design						
Randomized trial	65	22,768	1,172	5.1	230	1.0
Cohort or case-series study	55 (52)	22,760 (22,382)	1,020	4.5	269	1.2
Data collection dates[c]						
Before mifepristone registration	42 (41)	13,859 (13,608)	744	5.4	140	1.0
After mifepristone registration	44 (42)	22,029 (21,902)	864	3.9	245	1.1
Missing	34	9,640	584	6.1	114	1.2
Geographic region						
Europe	31 (30)	10,772 (10,745)	378	3.5	88	0.8
Americas	36	16,598	564	3.4	123	0.7
Other	53 (51)	18,158 (17,807)	1,250	6.9	288	1.6
Number of study sites						
1	59 (57)	12,071 (11,944)	452	3.7	102	0.9
>1	61 (60)	33,457 (33,206)	1,740	5.2	397	1.2
Prescribed interval between mifepristone and misoprostol						
<23 h	11	2,018	108	5.4	20	1.0
23–72 h	109 (106)	43,510 (43,132)	2,084	4.8	479	1.1
Protocol specified additional dose of misoprostol for selected subjects						
No	67 (64)	20,512 (20,134)	1,335	6.5	276	1.4
Yes	53	25,016	857	3.4	223	0.9
Protocol required all subjects to take misoprostol in clinic						
No	56 (55)	24,921 (24,894)	1,132	4.5	306	1.2
Yes	57 (56)	18,007 (17,907)	930	5.2	178	1.0
Not stated	7 (6)	2,600 (2,349)	130	5.0	15	0.6
Minimum scheduled follow-up interval						
<1 week	36	15,343	485	3.2	90	0.6
≥1 week	84 (81)	30,185 (29,807)	1,707	5.7	409	1.4
Protocol required ultrasound to assess failure						
In none or some subjects	51 (50)	26,505 (26,478)	1,472	5.6	365	1.4
In all subjects	64 (63)	18,046 (17,946)	647	3.6	121	0.7
Not stated	5 (4)	977 (726)	73	7.5	13	1.8
% of population who were nulliparous						
>50%	34 (33)	15,522 (15,271)	563	3.6	89	0.6
≤50%	40 (39)	16,378 (16,278)	838	5.1	203	1.2
Missing	46 (45)	13,628 (13,601)	791	5.8	207	1.5
% of population with gestational age >56 days						
>25%	16	8,579	506	5.9	87	1.0
≤25%	84 (82)	33,123 (32,996)	1,506	4.5	380	1.2
Missing	20 (19)	3,826 (3,575)	180	4.7	32	0.9
Misoprostol dose and route[d]						
200 mcg oral	1	4	1	25.0	1	25.0
400 mcg buccal	1	272	8	2.9	4	1.5
400 mcg oral	21	9,299	737	7.9	215	2.3
400 mcg sublingual	10	2,875	126	4.4	30	1.0
400 mcg vaginal	5	1,116	86	7.7	20	1.8
600 mcg oral	9	1,608	132	8.2	22	1.4
600 mcg sublingual	4	540	7	1.3	0	0.0
600 mcg vaginal	1	242	18	7.4	9	3.7
≥800 mcg buccal	6	2,205	71	3.2	16	0.7
≥800 mcg oral	10 (8)	2449 (2,322)	158	6.5	38	1.6
≥800 mcg sublingual	4	1,003	52	5.2	5	0.5
≥800 mcg vaginal	43 (42)	19,210 (18,959)	653	3.4	99	0.5
Varied or missing	5	4,705	143	3.0	40	0.9

[a] Number in all groups (number in groups in which ongoing pregnancy was reported, if different).
[b] Percent of subjects in trial groups reporting outcome.
[c] Dates of mifepristone registration in each country obtained from www.gynuity.org, accessed 17 August 2011. Coded as "before mifepristone registration" if the year that data collection ended was not more than 1 year after the registration year and otherwise as "after" if the data collection started in the year after the registration year or later. This variable is missing for trials conducted in multiple countries and studies that provided insufficient information about dates of data collection.
[d] Total misoprostol dose and route of first dose if multiple doses were administered.

Table 2
Associations between trial and population characteristics and rates of medical abortion failure and ongoing pregnancy[a]

	Medical abortion failure rate		Ongoing pregnancy rate	
	OR	(95% CI)	OR	(95% CI)
Group size: each increase of 500 women	1.0	(0.9–1.1)	1.0	(0.9–1.2)
Study design				
Randomized trial	1.1	(0.9–1.4)	1.2	(0.8–1.9)
Cohort or case-series study	1		1	
Data collection dates[b]				
Before mifepristone registration	1.2	(0.8–1.6)	0.7	(0.3–1.5)
After mifepristone registration	1		1	
Geographic region				
Europe	0.7	(0.4–1.3)	0.6	(0.3–1.3)
Americas	1		1	
Other	1.0	(0.7–1.5)	0.9	(0.4–1.7)
Number of study sites				
1	0.9	(0.7–1.3)	0.8	(0.5–1.2)
>1	1		1	
Prescribed interval between mifepristone and misoprostol				
<23 h	2.1	(1.4–3.2)	1.2	(0.5–2.9)
23-72 h	1		1	
Protocol specified additional dose of misoprostol for selected subjects				
Yes	0.7	(0.5–1.1)	1.1	(0.6–2.0)
No	1		1	
Protocol required all subjects to take misoprostol in clinic				
No	0.9	(0.7–1.2)	1.3	(0.7–2.7)
Yes	1		1	
Minimum scheduled follow-up interval				
<1 week	0.9	(0.7–1.2)	1.4	(0.6–3.0)
≥1 week	1		1	
Protocol required ultrasound to assess failure				
Never or in selected subjects	1.1	(0.7–1.7)	2.0	(1.0–3.9)
In all subjects	1		1	
% of population who were nulliparous				
>50%	1.1	(0.9–1.4)	0.8	(0.5–1.3)
≤50%	1		1	
% of population with gestational age >56 days				
>25%	1.5	(1.1–2.0)	0.9	(0.6–1.6)
≤25%	1		1	
Lost to follow-up %: each 1% increase	0.6	(0.0–25.2)	5.9	(0.0–4,524)
Misoprostol route by dose[c]				
400 mcg				
Sublingual	0.5	(0.4–0.7)	0.5	(0.3–0.7)
Buccal	0.5	(0.3–0.8)	0.5	(0.2–1.0)
Vaginal	0.6	(0.4–1.0)	0.7	(0.4–1.3)
Oral	1		1	
600 mcg				
Sublingual	0.2	(0.1–0.3)	–	
Vaginal	0.5	(0.2–0.9)	4.6	(1.2–18.0)
Oral	1		1	
≥800 mcg				
Sublingual	0.6	(0.4–0.9)	0.3	(0.2–0.6)
Buccal	0.6	(0.4–0.9)	0.3	(0.2–0.6)
Vaginal	0.6	(0.5–0.8)	0.4	(0.3–0.6)
Oral	1		1	
Misoprostol dose by route[c]				
Oral route				
≥800 mcg	0.7	(0.5–0.9)	0.6	(0.3–1.1)
600 mcg	0.9	(0.7–1.3)	0.6	(0.3–1.2)
400 mcg	1		1	
Vaginal route				
≥800 mcg	0.6	(0.4–0.9)	0.3	(0.2–0.6)
600 mcg	0.7	(0.4–1.2)	3.6	(1.2–11.5)
400 mcg	1		1	
Sublingual route				
≥800 mcg	0.8	(0.6–1.1)	0.4	(0.2–0.8)
600 mcg	0.3	(0.2–0.6)	–	
400 mcg	1		1	
Buccal route				
≥800 mcg	0.7	(0.5–1.2)	0.4	(0.2–0.8)
400 mcg	1		1	

[a] Analyses of medical abortion failure used 119 trial groups; analyses of ongoing pregnancy used 112 trial groups (see text).
[b] Dates of mifepristone registration in each country obtained from www.gynuity.org, accessed 17 August 2011. Coded as "before mifepristone registration" if the year that data collection ended was not more than 1 year after the registration year and otherwise as "after" if the data collection started in the year after the registration year or later. This variable is missing for trials conducted in multiple countries and studies that provided insufficient information about dates of data collection.
[c] Total misoprostol dose and route of first dose if multiple doses were administered.

pregnancy or other conditions unrelated to the abortion. Forty-five women (0.1%) received blood transfusions. Hospitalizations and blood transfusions were less common in trials in which women were permitted to take the misoprostol at home (0.15% and 0.08%, respectively) than in trials in which clinic administration was required (0.45% and 0.14%, respectively).

4. Discussion

Medical abortion using mifepristone 200 mg followed by misoprostol in the first 63 days of gestation is remarkably effective and safe. In trials that together included more than 45,000 women conducted in disparate settings over nearly two decades using a variety of regimens and treatment protocols, fewer than 5% of subjects required surgery to complete termination of the pregnancy. The proportion who had ongoing pregnancy at follow-up — the outcome of greatest concern to clinicians — was 1.1%. Serious complications requiring hospitalization or transfusion occurred in less than 0.4% of patients.

Some random variability in results is expected in any collection of research studies. However, our analysis found strong evidence of statistical heterogeneity across trials in both medical abortion failure rates and rates of ongoing pregnancy. This finding indicates that the non-uniformity in these outcomes was due to underlying differences among the studies rather than simply to chance. We identified a few practices that were associated with a lower risk of medical

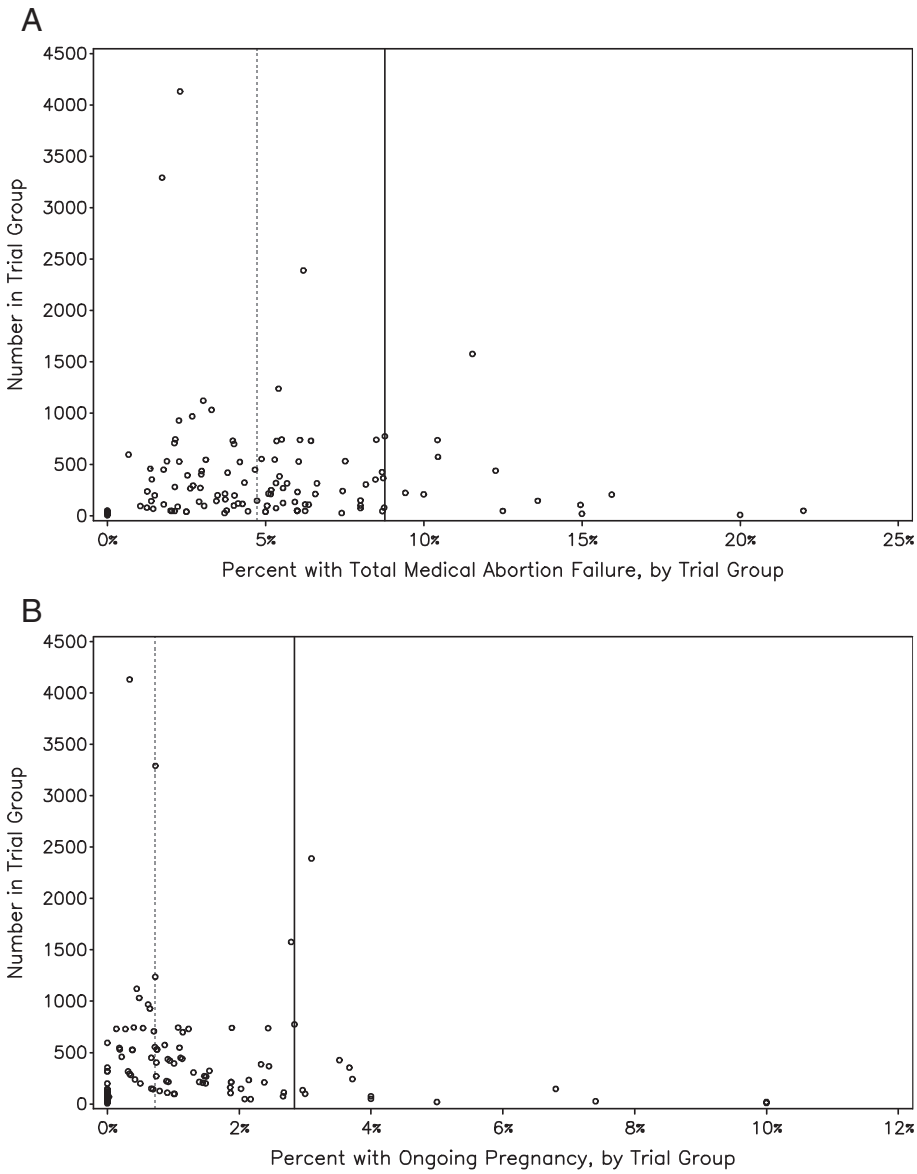

Fig. 1. Size of trial group by percentage of subjects with medical abortion failure and ongoing pregnancy at follow-up assessment. 50% of trial groups are to the left of dashed line; 90% of subjects are to the left of solid line. One group of 4 subjects with one ongoing pregnancy is omitted from both panels; panel A also omits one group of 20 subjects with 8 medical abortion failures. (A) Medical abortion failure. (B) Ongoing pregnancy.

abortion failure: an interval of at least 24 h between the mifepristone and misoprostol, use of misoprostol doses higher than 400 mcg and administration of misoprostol by a buccal, vaginal, or sublingual rather than oral route. The last of these is consistent with the conclusions of a recent Cochrane review of first trimester medical abortion, which included only randomized trials [89]. As cited previously, most current guidelines for medical abortion incorporate these practices.

We also found slightly higher risks of medical abortion failure in groups that had a high proportion (>25%) of women in the 9th week of pregnancy: after adjustment for other factors, these groups overall had a 50% higher odds of medical abortion failure. However, we did not find a higher risk of ongoing pregnancy in these groups. Given the low overall risk of medical abortion failure and the relative ease of treating failure using surgical evacuation (which would have been the treatment for all subjects had medical abortion not been attempted), offering medical abortion to women at this gestational age seems reasonable.

We observed no significant association between abortion failure rates and the timing of the follow-up evaluation. The data thus are inconclusive with respect to the theory that high surgical intervention rates are in part attributable to impatience among providers and patients [90]. Moreover, although routine ultrasound evaluation at follow-up was

associated with a lower risk of diagnosis of ongoing pregnancy, we found no evidence for or against an effect of this practice on overall medical abortion failure rates — that is, the need for surgical intervention. Prompt confirmation of completeness of the abortion and clinical assessment without routine ultrasound may enhance women's satisfaction with the procedure.

We found no evidence that allowing women to take the misoprostol at home increased the rates of abortion failure or serious complications. Most women prefer this option [90], and it is presumably substantially more efficient for the health care system than requiring patients to return to the provider for administration of the prostaglandin. This requirement, which is law in some countries such as the United Kingdom [7], thus is unjustifiable and should be abandoned.

This analysis has some limitations. Our data allowed us to explore heterogeneity across patient populations, not across individual patients; therefore, we may have missed some associations that would have been identified in an individual-level analysis. Missing data on some characteristics of some groups may have affected the direction or strength of associations, and we acknowledge that including "missing" categories for predictor variables would not have been preferred had we analyzed individual-level data [91]. Because none of the 540 women in the four groups that received misoprostol 600 mcg sublingual had ongoing pregnancies, these groups were excluded for technical reasons from our regression analysis of that outcome; this omission may have affected the apparent associations of other factors with ongoing pregnancy. Undetected publication bias is always possible; we attempted to minimize this problem by consulting experts likely to be aware of relevant unpublished studies through their many years of work in this field. We had information on only selected characteristics of the studies, and unmeasured confounding was not controlled by randomization. We evaluated many potential associations without any adjustment for multiple comparisons; however, we fit only a single model for each outcome. In 5 of the 120 trial groups, at least 10% of subjects were lost to follow-up. However, the overall follow-up success was high, and even if we made the extreme assumption that all the subjects who were lost had abortion failures, the overall medical abortion failure rate would still have been low (8.3%).

The large quantity of data presented in this review demonstrates that currently used medical abortion regimens are so effective and safe that additional research aimed at further clinical improvement will have little public health benefit. Future investigations should focus on service delivery issues: increasing access, reducing cost, enhancing patient comfort and ensuring availability of ancillary services such as contraception that can aid women in reaching their reproductive goals.

Acknowledgments

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Reprints will not be available.

Appendix. Selected data from 120 trial groups

Ref	Country	Date	Dose/route	Delay	Treated	Evaluable	Medical abortion failure		Ongoing pregnancy	
					N	N	N	%	N	%
11	Ethiopia	2009	800 mg vag	48	251	251	13	5.2	n/a	n/a
87	USA	2006–2007	800 mg buc	24 to 36	482	421	16	3.8	4	1.0
87	USA	2006–2007	800 mg oral	24 to 36	480	426	37	8.7	15	3.5
86	Nepal	2009–2010	800 mg vag	48	1077	1032	34	3.3	5	0.5
85	Multiple	2003–2005	800 mg vag	48	545	532	40	7.5	4	0.8
85	Multiple	2003–2005	800 mg vag	24	542	529	32	6.0	4	0.8
84	Multiple	2007–2008	400 mg SL	24	751	741	63	8.5	14	1.9
84	Multiple	2007–2008	400 mg vag	24	751	738	77	10.4	18	2.4
84	Multiple	2007–2008	800 mg SL	24	752	739	45	6.1	4	0.5
84	Multiple	2007–2008	800 mg vag	24	751	744	41	5.5	8	1.1
83	Multiple	1998–2000	800 mg oral then 400 mg oral bid×7 d	36 to 48	740	730	47	6.4	9	1.2
83	Multiple	1998–2000	800 mg vag then 400 mg oral bid×7 d	36 to 48	741	731	29	4.0	1	0.1
83	Multiple	1998–2000	800 mg vag	36 to 48	738	729	39	5.3	2	0.3
82	Taiwan	2000	400 mg, route n/a	48	20	20	8	40.0	1	5.0
82	Taiwan	2000	600 mg, route n/a	48	20	20	3	15.0	2	10.0
81	N. Korea	2007–2008	400 mg SL	48	199	199	8	4.0	0	0.0
80	UK	n/a	600 mg oral	48	100	100	8	8.0	3	3.0
79	China	n/a	400 mg vag	48	100	98	3	3.1	1	1.0

(*continued*)

Ref	Country	Date	Dose/route	Delay	Treated	Evaluable	Medical abortion failure		Ongoing pregnancy	
					N	N	N	%	N	%
78	China	n/a	800 mg SL	48	100	99	5	5.1	1	1.0
77	China	n/a	800 mg oral then 400 mg oral bid×7 d	48	50	48	3	6.3	0	0.0
77	China	n/a	800 mg vag then 400 mg oral bid×7 d	48	50	50	3	6.0	2	4.0
77	China	n/a	800 mg vag	48	50	47	1	2.1	0	0.0
76	China	n/a	400 mg vag	48	200	200	3	1.5	1	0.5
75	China	n/a	400 mg vag then 400 mg oral bid×14 d	48	20	20	0	0.0	0	0.0
74	China	n/a	800 mg SL	48	112	112	2	1.8	0	0.0
74	China	n/a	800 mg vag	48	112	112	7	6.3	3	2.7
73	India	n/a	600 mg oral	48	51	50	11	22.0	0	0.0
14	India	n/a	200 mg SL×3 q6h	24	40	40	0	0.0	0	0.0
72	Nepal	2009	600 mg oral	48	50	50	3	6.0	0	0.0
71	USA	2001–2003	400 mg oral	48	376	354	30	8.5	13	3.7
70	Canada	2001	400 mg oral	24 to 48	319	319	17	5.3	0	0.0
70	Canada	2001	600 mg oral	24 to 48	319	317	21	6.6	1	0.3
70	Canada	2001	800 mg vag	24 to 48	318	317	18	5.7	0	0.0
69	USA	n/a	800 mg vag	0	80	80	7	8.8	0	0.0
66	USA	1998–1999	800 mg vag	24	745	708	15	2.1	5	0.7
66	USA	1998–1999	800 mg vag	72	772	699	28	4.0	8	1.1
66	USA	1998–1999	800 mg vag	48	778	745	16	2.1	3	0.4
67	USA	2000	400 mg oral×2 q2h	48	279	270	15	5.6	2	0.7
67	USA	2000	400 mg oral	48	228	223	21	9.4	2	0.9
67	USA	2000	800 mg vag	48	538	528	12	2.3	2	0.4
68	USA	1999–2000	400 mg oral×2 q2h	24	561	548	29	5.3	6	1.1
68	USA	1999–2000	800 mg vag	24	607	596	4	0.7	0	0.0
65	USA	1997–1999	800 mg vag	48	1137	1121	34	3.0	5	0.4
64	USA	1999	800 mg vag	48	30	27	2	7.4	2	7.4
63	USA	1996–1997	800 mg vag	48	933	928	21	2.3	6	0.6
62	China	n/a	600 mg oral	48	149	148	7	4.7	3	2.0
61	Moldova	2005–2006	400 mg oral	24	240	233	14	6.0	5	2.1
61	Moldova	2005–2006	400 mg SL	24	240	238	3	1.3	1	0.4
60	Moldova	2007–2009	400 mg buc	24	277	272	8	2.9	4	1.5
60	Moldova	2007–2009	400 mg SL	24	273	267	7	2.6	4	1.5
59	USA	n/a	800 mg vag	6 to 8	40	40	1	2.5	0	0.0
58	USA	1998–2000	800 mg vag	48	28	28	0	0.0	0	0.0
57	USA	2008	800 mg vag or buc	0 to 72	139	135	8	5.9	4	3.0
10	UK	n/a	200 mg oral	48	4	4	1	25.0	1	25.0
10	UK	n/a	400 mg oral	48	10	10	2	20.0	1	10.0
10	UK	n/a	600 mg oral	48	7	7	0	0.0	0	0.0
56	Vietnam	2001	400 mg oral	48	1601	1577	182	11.5	44	2.8
55	Vietnam	2007–2008	800 mg buc	24	201	201	7	3.5	3	1.5
54	USA	2003	800 mg vag	0	40	40	2	5.0	0	0.0
53	India	2004–2005	400 mg SL	48	149	144	2	1.4	1	0.7
52	USA	2001–2004	800 mg buc	24 to 48	223	216	11	5.1	2	0.9
52	USA	2001–2004	800 mg vag	24 to 48	219	213	14	6.6	4	1.9
51	UK	n/a	600 mg oral	48	110	110	7	6.4	1	0.9
50	USA	2006	800 mg buc	0	120	117	5	4.3	0	0.0
15	Taiwan	2002–2005	600 mg SL	48	356	355	5	1.4	0	0.0
49	Taiwan	2005–2009	600 mg vag	0	254	242	18	7.4	9	3.7
48	Taiwan	2005–2006	800 mg vag	0	90	90	2	2.2	0	0.0
47	Sweden	2004–2007	800 mg vag	36 to 48	395	395	10	2.5	4	1.0
46	Nepal	2007–2008	400 mg oral	48	400	367	32	8.7	9	2.5
45	USA	n/a	800 mg vag	48	125	121	5	4.1	0	0.0
18	Finland	2000–2002	400 or 800 mg vag	24, 48, or 72	1289	1238	67	5.4	9	0.7
16	UK	2002–2003	600 mg SL	36 to 48	49	49	1	2.0	0	0.0
44	UK	2002–2003	600 mg SL then 400 mg SL 3 h later	36 to 48	57	53	0	0.0	0	0.0
44	UK	2002–2003	800 mg vag then 400 mg vag 3 h later	36 to 48	72	69	1	1.4	0	0.0
17	UK	n/a	600 mg SL	36 to 48	96	96	1	1.0	0	0.0
17	UK	n/a	800 mg vag	36 to 48	53	53	2	3.8	0	0.0
43	Tunisia	2000–2001	400 mg oral	48	332	323	14	4.3	5	1.5

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Ref	Country	Date	Dose/route	Delay	Treated	Evaluable	Medical abortion failure		Ongoing pregnancy	
					N	N	N	%	N	%
42	UK	2003–2005	800 mg vag	6	210	210	21	10.0	5	2.4
42	UK	2003–2005	800 mg vag	36 to 48	215	215	8	3.7	3	1.4
41	India	2009–2010	400 mg vag	0	40	40	2	5.0	0	0.0
41	India	2009–2010	400 mg vag	24	40	40	1	2.5	0	0.0
40	USA	n/a	800 mg vag	6 to 8	80	80	1	1.3	0	0.0
39	Tunisia	2007–2008	400 mg oral	48	126	126	7	5.6	1	0.8
38	Vietnam, Tunisia	1997–1998	400 mg oral	48	315	306	25	8.2	4	1.3
37	UK	n/a	400 mg oral×2 q2h	36 to 48	75	75	6	8.0	3	4.0
37	UK	n/a	800 mg oral	36 to 48	75	75	4	5.3	2	2.7
36	USA	1998–1999	800 mg vag	24, 48, or 72	138	138	4	2.9	0	0.0
8	India	n/a	400 mg oral	24	48	48	6	12.5	1	2.1
8	India	n/a	400 mg SL	24	45	45	2	4.4	0	0.0
35	India	n/a	800 mg vag	48	50	50	1	2.0	0	0.0
34	USA	2004–2006	800 mg vag	0	567	554	27	4.9	4	0.7
34	USA	2004–2006	800 mg vag	23 to 25	561	546	17	3.1	1	0.2
33	USA	2000–2001	800 mg vag	24 to 48	148	145	5	3.4	0	0.0
9	USA	2002–2003	800 mg vag	23 to 25	539	531	10	1.9	1	0.2
9	USA	2002–2003	800 mg vag	6 to 8	539	525	22	4.2	2	0.4
32	India	2004–2005	400 mg oral×2 q3h	48	150	150	12	8.0	1	0.7
32	India	2004–2005	400 mg oral	48	150	147	20	13.6	10	6.8
12	France	2001–2002	400 mg oral×2 q24h	24	30	27	1	3.7	n/a	n/a
31	USA	2005–2007	800 mg vag, oral or buc	6 to 72	4087	3292	57	1.7	24	0.7
30	Nepal	2004–2005	400 mg oral	48	112	107	16	15.0	2	1.9
29	Nepal	2005–2006	800 mg vag	48	50	50	3	6.0	0	0.0
27	Albania	2001–2003	400 mg oral	48	409	404	12	3.0	3	0.7
28	India	2007–2008	400 mg oral	48	599	574	60	10.5	5	0.9
26	Curacao	2009–2010	800 mg buc	24 to 36	304	281	6	2.1	1	0.4
25	Tunisia	1999–2000	400 mg oral	48	222	213	11	5.2	4	1.9
24	India	n/a	600 mg oral	48	450	440	54	12.3	5	1.1
23	UK	n/a	800 mg vag	48	500	459	6	1.3	1	0.2
22	UK	n/a	600 mg oral	48	400	386	21	5.4	9	2.3
21	UK	1994–2001	800 mg vag	36 to 48	4132	4132	95	2.3	14	0.3
13	India	2003–2004	800 mg oral	24	100	100	4	4.0	n/a	n/a
20	Turkey	2004–2005	400 mg oral	48	161	161	6	3.7	3	1.9
20	Turkey	2004–2005	400 mg SL	48	46	46	4	8.7	1	2.2
19	Turkey	2000–2001	400 mg oral	48	208	207	33	15.9	3	1.4
88	multiple	n/a	400 mg oral	48	792	775	68	8.8	22	2.8
U1	Mexico	2010–2011	800 mg buc	24 to 48	998	969	26	2.7	6	0.6
U2	Ukraine	2005–2007	400 mg oral	48	439	436	13	3.0	4	0.9
U3	Uzbekistan	2008–2009	400 mg SL	24	450	450	21	4.7	5	1.1
U4	Moldova	2007	400 mg SL	24	300	295	8	2.7	1	0.3
U5	Vietnam	2006–2008	400 mg oral	48	2400	2389	148	6.2	74	3.1
U6	Ukraine	2007–2009	400 mg SL	24	450	450	8	1.8	3	0.7

n/a: data not available.

Ref indicates reference number. U1-U6 are unpublished studies.

Date indicates dates of data collection.

Dose/route indicates dose and route of misoprostol. SL, sublingual; vag, vaginal; buc, buccal; q, every; h, hours; d, days.

Delay indicates prescribed interval between mifepristone and misoprostol, in hours.

Evaluable indicates number of subjects with known abortion outcome.

Failures indicates number and percent of evaluable subjects with abortion failure.

Ongoing pregnancy indicates number and percent of evaluable subjects with abortion failures that were ongoing pregnancies.

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