Efficacy of Misoprostol Alone for First-Trimester Medical Abortion

A Systematic Review

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OBJECTIVE: To summarize available data on the effectiveness and safety of single-agent misoprostol for medical abortion in the first trimester.

DATA SOURCES: We searched MEDLINE, CABI, Cochrane, EMBASE, LILACS, the Web of Science, and ClinicalTrials.gov for English-language studies that evaluated misoprostol alone for abortion of a viable pregnancy in the first trimester.

METHODS OF STUDY SELECTION: Our search yielded 1,562 citations, of which 38 included data from 53 trial groups that met our inclusion and exclusion criteria.

TABULATION, INTEGRATION, AND RESULTS: We abstracted data about each trial group, including study characteristics, treatment regimen, clinical protocol, number of women treated and followed, and numbers with outcomes of interest. We used meta-analytic methods and logistic regression to examine factors associated with surgical intervention after treatment. Among all 12,829 evaluable women, 2,536 (meta-analytic estimate 22.0%, 95% CI 18.8–25.5%) had surgical uterine evacuation. Multiple factors were significantly associated with this proportion, including misoprostol amount per dose and route of administration, loss to follow-up rate, publication date, geographic region, number of misoprostol doses, duration of dosing, and time between dosing and evaluation. Of 6,359 evaluable women, 384 (meta-analytic estimate 6.8%, 95% CI 5.3–8.5%) had ongoing pregnancies. At most 26 of 12,184 evaluable women (meta-analytic estimate 0.7%, 95% CI 0.4–1.0%) were transfused or hospitalized for abortion-related reasons. In trials that provided satisfaction data, most women were satisfied or very satisfied with the treatment (meta-analytic estimate 78%, 95% CI 71–85%).

CONCLUSIONS: Misoprostol alone is effective and safe and is a reasonable option for women seeking abortion in the first trimester. Research is indicated to further refine the regimen and to establish efficacy in the late first trimester.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO, CRD42018083589.

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For early medical abortion, the primary regimens recommended by current clinical guidelines include two drugs: mifepristone and misoprostol. Because mifepristone potentiates the abortifacient action of misoprostol, the combination is highly effective, resulting in complete abortion in more than 95% of women through 63 days of gestation[1,2] and 93% between 64 and 70 days.[2,3] However, mifepristone is costly and is unavailable in many settings. In the United States, although the drug is approved for marketing, the U.S. Food and Drug Administration has imposed restrictions on its distribution that substantially limit both patients' and health care providers' access to it.[4] For women who cannot obtain mifepristone, use of misoprostol alone, which is inexpensive and is widely used for various obstetric and gastrointestinal indications, can serve as an important alternative option. A systematic review published in

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2007 found that the efficacy of misoprostol single-agent regimens at gestational ages 63 days or less ranged from 84% to 96%,[5] but since then, additional studies have been published. We performed this systematic review to summarize available data on the effectiveness and safety of medical abortion with misoprostol alone in the first trimester of pregnancy. The primary outcome of our analysis was surgical evacuation of the uterus to complete the abortion; secondary outcomes were a viable ongoing pregnancy after taking the prescribed misoprostol regimen, transfusions, and hospitalizations.

SOURCES

We registered our systematic review protocol on PROSPERO (CRD42018083589) before beginning data collection and followed Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines[6] in reporting the results. With the assistance of a librarian, we searched six databases (MEDLINE, CABI, Cochrane, EMBASE, LILACS, and the Web of Science) on November 17, 2017, and ClinicalTrials.gov on June 20, 2018, for English-language studies that evaluated misoprostol alone for medical abortion of a known or presumed viable pregnancy in the first trimester. We did not exclude studies based on study design, date, or any other criteria. Our search strategy for MEDLINE is indicated in Box 1.

Search strategies for other databases were substantively similar. 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.

STUDY SELECTION

Two authors (M.S.H. and E.G.R.) separately reviewed the title, abstract, and full text if necessary of each article identified by the search to select all language reports of studies that included women with viable pregnancies who were treated in the first trimester (91 days of gestation or less) with misoprostol alone to cause abortion. The same two authors then reviewed each selected study together and systematically abstracted relevant data about these women into a custom database. We excluded women who received abortifacient drugs other than misoprostol, women who were treated in the second trimester, women who had missed abortions or nonviable pregnancies before treatment, and women who did not take any misoprostol after study enrollment. Some studies evaluated more than one misoprostol regimen; in our abstraction process, we recorded data about women who received each regimen in each study as a separate trial group.

Box 1. Search Strategy for MEDLINE

(Early trimester OR less than ten weeks OR early pregnancy OR first trimester OR less than thirteen weeks) AND (Medical abortion OR medical termination OR oral medication abortion OR oral medication termination OR non-surgical abortion OR non-surgical termination OR elective abortion OR termination of pregnancy OR induced abortion OR induced termination of pregnancy) AND (misoprostol OR cytotec) AND (single agent OR single-agent OR alone OR only)

The primary data abstracted included the number of women treated with the misoprostol regimen in each group, details of the misoprostol regimen (specifically, the number of misoprostol doses provided, the amount of misoprostol in each dose and route of administration, and the intervals between doses), abortion outcomes (specifically, whether surgical evacuation of the uterus was performed and whether the patient had a viable ongoing pregnancy at the time of surgery), the numbers of reported hospitalizations and transfusions, and information about patient satisfaction. We also recorded data about specified factors that we postulated could cause heterogeneity or bias in assessment of efficacy and safety, including information about the trial design, conduct, and publication, the maximum gestational age and other inclusion criteria, location of misoprostol administration (facility or home), follow-up rates, and timing and method of outcome assessment. We contacted some authors to obtain additional data or to clarify details about the studies. We used our judgment to interpret certain details in some reports and to correct apparent errors and inconsistencies.

We combined data across groups to estimate the proportion of patients who had surgical evacuation of the uterus to complete the abortion and viable ongoing pregnancy using meta-analytic methods, conducted in R 3.5.0, with the "metafor" package 2.0.[7] We applied the Freeman-Tukey double arcsine transformation, and we report P values from the χ^2 test of heterogeneity and associated I^2 statistic. We calculated estimates and 95% CIs using the DerSimonian-Laird random-effects model.

To explore possible explanations for heterogeneity among trial groups in the proportions who had surgery, we examined associations between this outcome and selected characteristics of the trial groups. Many of these characteristics were highly correlated across trial groups with numerous zero cells in cross-classifications. Therefore, we opted to present

only unadjusted results. We used generalized estimating equations with a logistic link and an independence working correlation matrix to control for nesting of trial groups within the article. The response for the models was the ratio of the number of surgeries to the number of evaluable patients for each trial group (conducted in SAS 9.4); thus, model results were weighted by trial group sample size. We included all trial groups in our examination of misoprostol amount per dose and route of administration. We restricted our examination of other factors to groups treated with an initial dose of 800 micrograms misoprostol administered vaginally, the most common combination, because most characteristics did not vary across groups treated with other dose–route combinations. We categorized each characteristic considering both clinical interest and the distribution of the data, and we estimated odds ratios (ORs) and 95% CIs. We tested for linear trends using linear contrasts of model parameters. We made no adjustment for multiple comparisons. In reviewing the results, we focused on associations that were both substantial (OR >1.5 or <0.67) and significant ($P<.05$).

To further evaluate the association between number of misoprostol doses and efficacy, we estimated the proportion of women reported to have had a complete abortion after taking only the doses required for all women in that trial group before any doses that were contingent on abortion status. This analysis included only those trial groups that reported these data. We estimated unadjusted ORs with CIs and tested for linear trend as described above for the amount of misoprostol in the initial dose.

We assessed safety by computing the proportion of women across all trial groups who were reported to have been hospitalized or receive transfusions after treatment. We did not abstract data on nonserious side effects because ascertainment and reporting were not standardized across studies.

RESULTS

Our search yielded 1,562 unique citations, of which 37 reported at least one group of women who were treated with misoprostol alone for abortion of a viable pregnancy at 91 days of gestation or less[8–44] and one additional group in which the maximum gestational age was 98 days[45] (Fig. 1). We included the last of these because most of the women in the study were 91 days of gestation or less; the mean gestational age was 64 days. We also identified one additional study (ClinicalTrials.gov Identifier: NCT02299401) that has to date been published only as an abstract, but the authors declined to provide final data for this review because of concern about jeopardizing the planned primary publication.

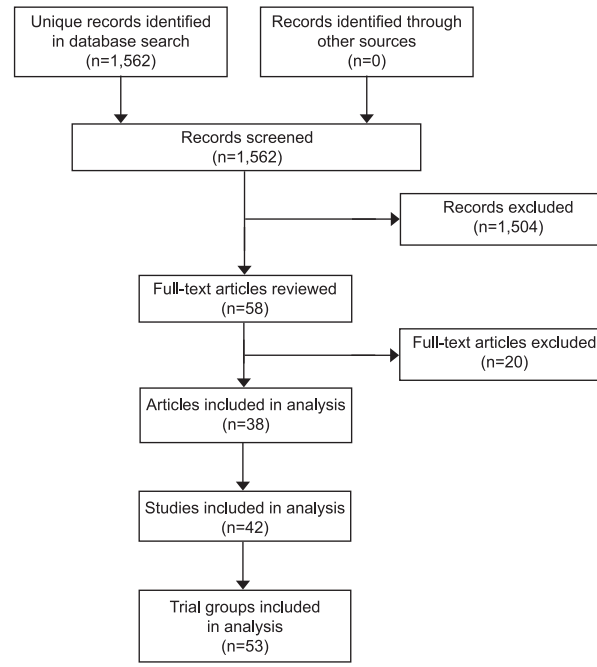

Fig. 1. Study selection flow diagram.
Raymond. Efficacy of Misoprostol for First-Trimester Abortion. Obstet Gynecol 2019.

The 38 articles included 42 studies conducted in at least 16 countries over at least the past 24 years (Appendix 1, available online at http://links.lww.com/AOG/B219). Of these studies, 21 were noncomparative case-series studies, seven were randomized trials or cohort studies comparing different misoprostol-only regimens, and 14 were randomized trials or cohort studies comparing misoprostol-only regimens to other abortion treatments (aspiration, methotrexate, or misoprostol combined with mifepristone, methotrexate, tamoxifen, letrozole, or laminaria).

The 42 studies included 53 trial groups of women treated with misoprostol alone (Table 1). The total number of treated patients in all groups combined was 13,573. The two largest groups, both retrospective case series in anonymous Latin American countries where abortion was legally restricted, constituted 44% of this total.[8,9] Over all groups, 744 women (5%) were lost before their abortion outcomes were ascertained. The proportion lost was 0–7% in 51 groups; the proportions in the other two groups, which were the two largest, were 10% and 13%. Our analysis included 12,829 evaluable women across all trial groups.

Table 1. Characteristics of Studies

Characteristic	Trial Groups (N=53)	Evaluable Women (N=12,829)
No. of treated women per group		
3–100	27 (51)	1,247 (10)
101–500	19 (36)	3,472 (27)
501–720	5 (9)	2,766 (22)
2,805–3,225	2 (4)	5,344 (42)
Lost to follow-up		
None	39 (74)	4,484 (35)
10% or less	12 (23)	3,001 (23)
More than 10%	2 (4)	5,344 (42)
Publication date		
1994–1999	14 (26)	1,609 (13)
2000–2004	14 (26)	5,093 (40)
2005–2009	18 (34)	5,237 (41)
2010–present	7 (13)	890 (7)
Study design		
Randomized trial	23 (43)	3,315 (26)
Nonrandomized prospective	24 (45)	3,527 (27)
Nonrandomized retrospective	6 (11)	5,987 (47)
Region		
Latin or South America	11 (21)	7,664 (60)
North America	11 (21)	1,023 (8)
Asia	17 (32)	980 (8)
Other or multiple	14 (26)	3,162 (25)
Planned maximum gestational age (d)		
42–56	19 (36)	4,173 (33)
57–63	17 (32)	4,563 (36)
64–70	7 (13)	3,247 (25)
71 or more	10 (19)	846 (7)
1st misoprostol dose (micrograms) and route		
200 vaginally	2 (4)	111 (1)
400 vaginally	4 (8)	160 (1)
600 vaginally	1 (2)	89 (1)
800 vaginally	31 (58)	10,010 (78)
800 buccally	3 (6)	584 (5)
800 sublingually	2 (4)	1,021 (8)
800 orally	4 (8)	119 (1)
1,000 vaginally	1 (2)	300 (2)
400 vaginally+400 sublingually	1 (2)	149 (1)
400 vaginally+400 orally	1 (2)	5 (0)
800 vaginally+400 buccally	1 (2)	98 (1)
800 vaginally+400 sublingually	1 (2)	76 (1)
800 orally+400 sublingually	1 (2)	107 (1)
Misoprostol moistened before vaginal administration*		
No or not stated	20 (47)	6,543 (59)
Yes	23 (53)	4,455 (41)
No. of required doses		
1	34 (64)	3,598 (28)
2	7 (13)	3,374 (26)
3	9 (17)	5,651 (44)
4	2 (4)	186 (1)
5	1 (2)	20 (0)
Duration of required dosing		
0 (only 1 required dose)	34 (64)	3,598 (28)
1–24 h	16 (30)	6,251 (49)
25–48 h	1 (2)	2,900 (23)
73 h to 7 d	2 (4)	80 (1)

(*continued*)

Table 1. Characteristics of Studies (*continued*)

Characteristic	Trial Groups (N=53)	Evaluable Women (N=12,829)
Total no. of allowed doses		
1	5 (9)	330 (3)
2	11 (21)	3,069 (24)
3	25 (47)	8,059 (63)
4	5 (9)	458 (4)
5	1 (2)	20 (0)
6	6 (11)	893 (7)
Maximum duration of dosing if all allowed contingent doses were taken		
0 (only 1 dose allowed)	5 (9)	330 (3)
1–24 h	19 (36)	4,995 (39)
25–48 h	13 (25)	5,682 (44)
49–72 h	4 (8)	269 (2)
73 h to 7 d	9 (17)	1,155 (9)
More than 7 d	3 (6)	398 (3)
Protocol permitted patient to take misoprostol at home		
All	9 (17)	5,188 (40)
Some	15 (28)	5,483 (43)
None	29 (55)	2,158 (17)
Evaluated by ultrasonography before decision to perform surgery		
All patients	46 (87)	10,199 (79)
Some or no patients	7 (13)	2,630 (21)
Earliest timing of decision re: surgery		
24 h or less	2 (4)	128 (1)
25–48 h	7 (13)	438 (3)
49–72 h	12 (23)	4,685 (37)
73 h to 7 d	16 (30)	1,864 (15)
More than 7 d	16	5,714 (45)

Data are n (%).
* Denominator for percents includes only trial groups and evaluable women who took the first dose by the vaginal route.

The admission criteria for all studies were broad: in general, any woman requesting medical abortion who had no medical contraindication to the abortifacient drug treatment and whose gestational age was less than a specified maximum (42–98 days of gestation) was eligible. In 48 groups, which included 95% of evaluable women, gestational age was routinely determined by ultrasonography. One study included only women aged 17 years or younger,[42] one included only women with two or more prior cesarean deliveries,[25] and one included only women with gestational ages of 64–84 days.[17]

The 53 groups used a multitude of misoprostol regimens. In all groups, women were required to take a specified minimum number (one to five) of doses of misoprostol vaginally, buccally, orally, sublingually, or by a combination of routes (Table 1). In all but four groups,[12,13,20] the initial dose was 800 micrograms or was administered vaginally; the combination 800 micrograms vaginally was used in 31 groups that collectively included 10,010 (78%) of the evaluable women. Misoprostol was moistened before vaginal insertion in 41% of evaluable women who took the drug by that route. In 39 of the 48 groups in which more than one dose was allowed, subsequent doses used the same amount per dose and route of misoprostol as the first dose. Multiple doses were administered 3–48 hours apart such that the longest duration of the required treatment was 96 hours. In 35 groups (38% of evaluable women), if complete abortion had not occurred after the required doses, women were instructed to take additional contingent doses up to a specified maximum, after which a decision regarding surgical intervention was made. The maximum total number of allowed doses (required+contingent) in any group was six, and the maximum duration of dosing if all allowed doses were taken was 14 days. Across all groups, most women were instructed to take no more than three doses within a maximum of 48 hours. Nine studies,[17–23,42,44] seven of which were conducted by the same group of investigators, provided extra misoprostol to some or all women who were determined not to need surgery; the purpose was to evacuate the "remains" from the uterus or for an unspecified reason. One study provided a dose of misoprostol to all women who were scheduled for

surgery.[29] We did not count those extra doses in this analysis because they were given after the outcome had been determined and thus did not contribute to the outcome. In at least 24 groups (83% of evaluable women), women were allowed to take some or all of the misoprostol doses at home.

In 46 groups (79% of evaluable women), all women were assessed with ultrasonography before the decision of whether to perform surgery; in six groups, ultrasonography was used only if clinically indicated; and in one group, abortions were provided by community health workers who apparently rarely used ultrasonography.[41] The earliest point at which surgical intervention was considered varied from 24 hours to 14 days after the first misoprostol dose. No article provided explicit criteria for the decision to resort to surgical uterine evacuation, hospitalization, or transfusion.

Among all 12,829 evaluable participants (Table 1), 2,536 (20%) underwent surgical uterine evacuation (meta-analytic estimate 22.0%, 95% CI 18.8–25.5%). Across trial groups, the proportion with this outcome ranged from 0% to 77% (Fig. 2A). More than 90% of the evaluable participants were in trial groups in which the failure proportion was 24% or less.

We found strong evidence of heterogeneity across trial groups in the proportion of participants who ultimately had surgery ($P<.001$, $I^2=94.2\%$). In unadjusted analyses, this proportion was significantly associated with characteristics of the initial misoprostol dose (Table 2). Among groups treated vaginally, the odds of surgery decreased with the amount of misoprostol in the initial dose (linear trend $P<.001$); groups treated with 800 micrograms or more had approximately one fourth the risk of surgery as groups treated with 200 micrograms. Among groups treated with 800 micrograms in the initial dose, oral administration was associated with nearly a threefold higher risk of surgery than vaginal administration, whereas risks were similar in groups who took the drug sublingually, buccally, and vaginally.

In the 31 groups treated initially with 800 micrograms vaginally, the proportion of women who had surgery was significantly associated with numerous group characteristics (Table 3). Some of these were details of the clinical protocol: the risk of surgery declined with increases in both the allowed number of misoprostol doses and the duration of dosing (linear trend $P\leq.01$ for both associations). Surgery was less common in groups in which the misoprostol was moistened before vaginal insertion and in groups in which the decision to perform surgery was delayed until 4–7 days after treatment. Surgery was also associated with other characteristics of the studies; for example, the two groups with loss rates greater than 10% had higher surgery rates than groups with no loss, later studies had higher rates than earlier ones, and studies conducted in Asia and Latin America had higher rates than those conducted in North America. Many of the group characteristics were correlated with each other: for example, groups that were given more doses also had longer duration of dosing and were more likely to use moistened tablets if the route of administration was vaginal, and both of the two studies with more than 10% loss took place in Latin America and did not report using moistened tablets.

Data on abortion status after only the required misoprostol doses were available from 42 trial groups (Table 4). In these groups, each woman was evaluated

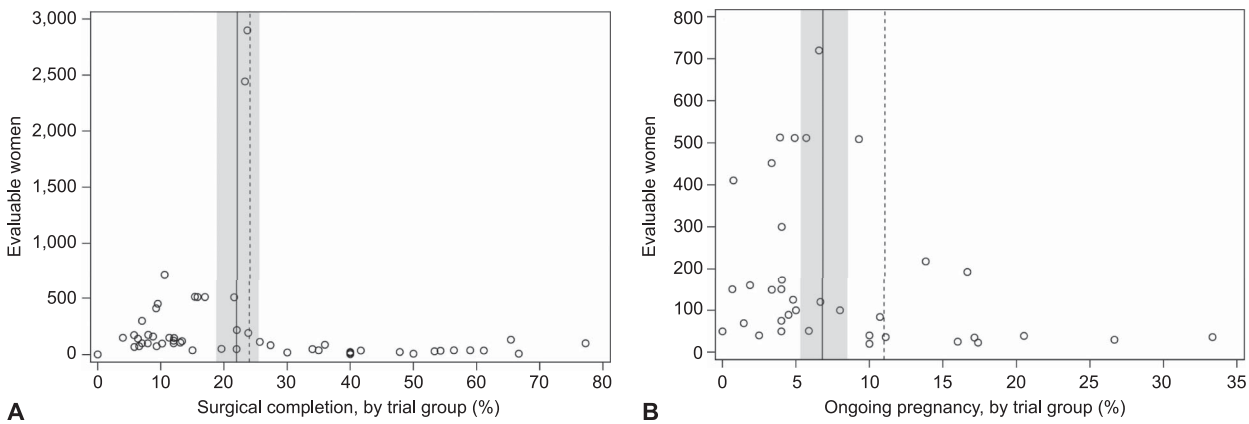

Fig. 2. Group size by percentage of women with surgical uterine evacuation (**A**) and ongoing pregnancy (**B**). Meta-analytic estimate of population proportion indicated by the *solid line* with 95% CI indicated by *band*. The trial groups to the left of the *dashed lines* contained 90% of patients.

Raymond. Efficacy of Misoprostol for First-Trimester Abortion. Obstet Gynecol 2019.

Table 2. Surgical Uterine Evacuation by Misoprostol Dose and Route*

	Evaluable Women	Women Who Had Surgical Uterine Evacuation	Adjusted OR (95% CI)†
1st dose administered vaginally			
200 micrograms	111	83 (75)	1
400 micrograms	160	99 (62)	0.55 (0.52–0.57)
600 micrograms	89	32 (36)	0.19 (0.14–0.26)
800 micrograms	10,010	1,895 (19)	0.08 (0.05–0.12)
1,000 micrograms	300	21 (7)	0.03 (0.02–0.04)
1st dose 800 micrograms			
Vaginal route	10,010	1,895 (19)	1
Buccal route	584	104 (18)	0.93 (0.49–1.76)
Sublingual route	1,021	191 (19)	0.99 (0.76–1.27)
Oral route	119	62 (52)	4.66 (3.61–6.01)
Combinations of routes	154	20 (13)	0.64 (0.46–0.89)

OR, odds ratio.
Data are n or n (%) unless otherwise specified.
* Table includes 53 trial groups.
† CIs are adjusted for clustering by article.

to determine abortion completeness after she took all of the required doses but before any additional doses. Complete abortion was significantly more common after three doses than after only one, but no significant linear trend was apparent by number of doses from one to five (P=.73).

In 36 groups, researchers noted the number of surgical interventions performed for ongoing pregnancy. Of the 6,359 evaluable women in these groups (50% of the total), 384 (6%) had ongoing pregnancies (meta-analytic estimate 6.8%, 95% CI 5.3–8.5%, heterogeneity: P<.001, I^2=81.7%). The proportion across groups ranged from 0% to 33%; more than 90% of the women were in groups in which no more than 11% of participants had ongoing pregnancy (Fig. 2B). The 384 ongoing pregnancies constituted 39% of the 989 medical abortion failures in these groups.

Across the 38 articles, 14 women were hospitalized for abortion-related reasons and 12 received transfusions. Excluding the studies in which women were or may have been hospitalized routinely throughout the abortion process,[12,13,17,25,26,32,45] the sum of these numbers (26) constitutes at most 0.2% of the total 12,184 evaluable women (meta-analytic estimate 0.7%, 95% CI 0.4–1.0%). No deaths or ectopic pregnancies were reported.

Women in 20 groups provided information about satisfaction about the treatment regimen (Appendix 1, http://links.lww.com/AOG/B219). In these groups, 2,549 of 2,961 women (86%; meta-analytic estimate 78%, 95% CI 71–85%) said that they were satisfied or very satisfied, and 2,396 of 2,832 (85%; meta-analytic estimate 76%, 95% CI 76–82%) said that they would use the method if needed in the future.

DISCUSSION

Data from 42 studies that included nearly 13,000 evaluable women indicate that misoprostol used alone can be effective and safe for inducing abortion in the first trimester. Across all studies, approximately 78% of women had complete abortions without recourse to surgery, and viable pregnancy was terminated in more than 93%. The reported incidence of serious complications requiring hospitalization or transfusion was at most 0.2%. Most women were satisfied with the treatment.

Our analysis identified some treatment characteristics that were associated with higher effectiveness. The chance of surgical uterine evacuation decreased significantly as the amount of misoprostol in the initial dose increased and was lower in trial groups that administered this dose vaginally, sublingually, or buccally rather than orally. Among groups in which the dose was 800 micrograms vaginally, surgical intervention was substantially less common if women were permitted to take at least four doses, if these doses were taken over an interval of more than 48 hours, and if the tablets were moistened before insertion. Among all 53 groups, 20 were treated with at least three doses, the first of which consisted of at least 800 micrograms misoprostol administered vaginally (moistened), sublingually, or buccally; of the 5,338 evaluable women in these groups, 87% aborted without surgery.

The data reviewed here have many strengths: the studies were conducted in numerous diverse settings, the study populations were typical abortion clients unselected except with respect to gestational age, and follow-up rates were high. The variety of regimens

Table 3. Surgical Uterine Evacuation by Trial Characteristics in Groups Treated With 800 Micrograms Misoprostol Vaginally

Characteristic	Trial Groups (n=31)	Evaluable Women (n=10,010)	Women Who Had Surgical Uterine Evacuation (n=1,895)	OR (95% CI)*
No. of treated women per group				
3–100	15	823	193 (23)	1
101–500	11	2,098	209 (10)	0.36 (0.21–0.61)
501–720	3	1,745	242 (14)	0.53 (0.30–0.93)
2,805–3,225	2	5,344	1,251 (23)	1.00 (0.62–1.60)
Lost to follow-up in group				
0	22	2,991	390 (13)	1
10% or less	7	1,675	254 (15)	1.19 (0.81–1.75)
More than 10%	2	5,344	1,251 (23)	2.04 (1.56–2.66)
Publication date				
1994–1999	8	1,342	164 (12)	1
2000–2004	12	4,704	859 (18)	1.60 (0.91–2.82)
2005–present	11	3,964	872 (22)	2.03 (1.39–2.96)
Study design				
Randomized	12	1,602	311 (19)	1
Prospective cohort or case series	15	2,603	284 (11)	0.51 (0.35–0.74)
Retrospective cohort or case series	4	5,805	1,300 (22)	1.20 (0.82–1.74)
Region				
North America	6	841	95 (11)	1
Asia	12	668	157 (24)	1.97 (1.25–3.11)
Latin or South America	8	7,102	1,426 (20)	2.41 (1.16–5.03)
Other or multiple	5	1,399	217 (16)	1.44 (0.95–2.20)
Planned maximum gestational age (d)				
42–56	14	3,905	743 (19)	1
57–63	11	2,742	380 (14)	0.68 (0.43–1.09)
63 or more	6	3,363	772 (23)	1.27 (0.85–1.89)
Misoprostol moistened before vaginal administration				
No or not stated	11	6,093	1,419 (23)	1
Yes	20	3,917	476 (12)	0.46 (0.35–0.60)
Total no. of allowed doses				
1	4	305	78 (26)	1
2	8	2,862	656 (23)	0.87 (0.47–1.60)
3	16	6,221	1,106 (18)	0.63 (0.30–1.31)
4 or more	3	622	55 (9)	0.28 (0.14–0.57)
Maximum duration of dosing if all allowed contingent doses were taken				
0 (only 1 dose allowed)	4	305	78 (26)	1
1–24 h	9	3,759	817 (22)	0.81 (0.42–1.54)
25–48 h	9	5,138	910 (18)	0.63 (0.29–1.37)
More than 48 h	9	808	90 (11)	0.36 (0.16–0.82)
Protocol permitted patient to take misoprostol at home				
All or some	13	8,558	1,663 (19)	1
None	18	1,452	232 (16)	0.79 (0.49–1.26)
Evaluated by ultrasonography before decision to perform surgery				
All patients	29	8,985	1,729 (19)	1
Some or no patients	2	1,025	166 (16)	0.81 (0.62–1.06)
Earliest timing of decision re: surgery				
72 h or less	10	4,403	893 (20)	1
73 h to 7 d	8	1,087	133 (12)	0.55 (0.31–0.96)
More than 7 d	13	4,520	869 (19)	0.94 (0.59–1.49)

OR, odds ratio.
Data are n or n (%) unless otherwise specified.
* CIs are adjusted for clustering by article.

Table 4. Complete Abortion After Required Misoprostol Doses by Number of Doses Required

No. of Required Misoprostol Doses	Groups (n=42)	Evaluable Women (n=12,072)	Complete Abortion Without Surgery (n=9,074)	OR (95% CI)*
1	25	3,232	2,221 (69)	
2	6	3,156	2,343 (74)	1.31 (0.98–1.75)
3	8	5,478	4,355 (79)	1.77 (1.30–2.40)
4	2	186	141 (76)	1.43 (0.49–4.16)
5	1	20	14 (70)	1.06 (0.89–1.27)

OR, odds ratio.
Data are n or n (%) unless otherwise specified.
* CIs are adjusted for clustering by article.

and clinical protocols used in the 42 included studies enabled us to examine multiple factors that may contribute to the likelihood of surgical intervention after treatment with misoprostol alone. Our analysis of all of these studies provides insights not available from only the seven individual studies published to date that directly compared different misoprostol-only regimens or protocols.

However, our analysis also had significant limitations. Two studies contributed 44% of the patients, and thus these studies dominated the analysis. We evaluated trial group characteristics, not data from individual women. Furthermore, we could examine only those characteristics that were reported consistently across studies, and because of the high degree of correlation between these characteristics across trial groups, we restricted our analysis primarily to groups treated with one particular misoprostol amount–route combination. We looked at each characteristic separately rather than simultaneously in an adjusted multivariable analysis, and as a result, the associations that we identified are certainly affected by confounding and should not be interpreted as proof of causality. For example, moistening of vaginally administered tablets was associated with higher numbers of allowed doses, and both were associated with lower surgery rates; our analysis did not establish the extent to which either factor may have been independently responsible for improved regimen effectiveness. Nevertheless, this finding is consistent with other data. In particular, wetting the tablets has been shown to improve vaginal absorption of misoprostol[46] and enhance cervical dilation before surgical abortion,[47] and two randomized trials have suggested that it decreases risk of surgical intervention in first-trimester medical abortion.[35,48] Our finding that surgery was less common in trial groups without loss to follow-up may be explained by the fact that indications for surgery (abortion failure, bleeding) prompt patients to seek care. It suggests that the true risk among all treated patients may be lower than our estimate.

Despite these limitations, currently available data suggest that misoprostol as a single agent is a reasonable option for women seeking abortion in the first trimester. This treatment is clearly less effective than standard regimens that also contain mifepristone,[1,2] and thus enhanced vigilance should be recommended to detect potential failures. Nevertheless, misoprostol alone may be preferred by some women because it may be easier to obtain, less costly, or have other advantages. Further research is indicated to refine the regimen, addressing issues such as the optimal misoprostol amount per dose and dosing intervals if the drug is administered sublingually or buccally, which may be more convenient for women than vaginal insertion, and the efficacy of these regimens in the late first trimester.

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