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Early abortion with buccal versus sublingual misoprostol alone: a multicenter, randomized trial☆,☆☆,★,★★

Wendy R. Sheldon [a,*], Jill Durocher [a], Ilana G. Dzuba [a], Heather Sayette [b], Roxanne Martin [a], Mónica Cárdenas Velasco [b], Beverly Winikoff [a]

[a] Gynuity Health Projects, 220 East 42nd Street, Suite 710, New York, NY, 10017
[b] Planned Parenthood Global, 123 William Street, New York, NY, 10038

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ABSTRACT

Objective: To compare efficacy, safety/side effects and acceptability of buccal versus sublingual administration of a misoprostol-only regimen commonly used for early medical abortion.
Study design: We conducted a randomized trial at six clinics in two Latin American countries. We randomized women seeking early abortion to buccal or sublingual administration of three doses of misoprostol 800 mcg repeated every 3 h. At initial follow-up (7–14 days after misoprostol), we offered women without a complete abortion aspiration or additional misoprostol plus waiting 7 more days. The primary outcome was continuing pregnancy at initial follow-up. Secondary outcomes included continuing pregnancy at final follow-up, incomplete abortion, successful abortion, side effects, acceptability and complications. We analyzed all outcomes as intention to treat.
Results: We enrolled 401 women and randomized 202 into the buccal arm and 199 into the sublingual arm. Continuing pregnancy at initial follow-up occurred in 11/201 (5.5%) and 2/189 (1.1%) women, respectively ($p=.02$). Additional misoprostol at follow-up increased success, defined as complete abortion, from 170/201 (84.6%) to 184/199 (92.5%) in the buccal arm and 165/189 (87.3%) to 177/189 (93.7%) in the sublingual arm. We found no differences by gestational age. Women reported similar acceptability and side effects across groups except for chills and fever, which women using sublingual misoprostol reported more frequently ($p<.05$).
Conclusions: Sublingual administration was superior to buccal administration in reducing continuing pregnancy risk after a three-dose regimen of 800 mcg misoprostol. Complete abortion rates were comparable across groups, and in both cases, additional misoprostol at follow-up increased success.
Implications: If the primary goal is to avoid continuing pregnancy, sublingual administration of misoprostol 800 mcg every 3 h for three doses should be recommended. If chills or fever are a concern and the primary goal is to avoid surgery, buccal administration may be preferable. For either route, additional misoprostol can be given for incomplete abortion or continuing pregnancy.

1. Introduction

Medical abortion, which involves pills rather than suction or sharp curettage, is a noninvasive procedure that is safe and highly effective [1–4]. Although mifepristone followed by misoprostol is the gold standard for early medical abortion, misoprostol alone is recommended for settings where mifepristone is unavailable [5,6]. While misoprostol alone is less effective than when taken in conjunction with mifepristone, it is often the next best option due to its safety, low cost and wide availability [7–9]. In most of Latin America, where abortion remains highly restricted and mifepristone is not approved, misoprostol use has been increasing since the 1990s and credited with improving abortion safety in the region [10–15].

At the time of this study, the World Health Organization (WHO) recommended misoprostol 800 mcg sublingually or vaginally every 3 to 12 h for a total of three doses for abortion through 12 weeks in settings without mifepristone [5]. The evidence for this recommendation came mainly from one large randomized trial that found similar efficacy (84% and 85%, respectively) and continuing pregnancy (6% and 4%, respectively) for both routes of administering this regimen [16].

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* Corresponding author. Tel.: +1 212 448 1230.
E-mail address: wsheldon@gynuity.org (W.R. Sheldon).

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For some women, however, vaginal administration is less acceptable than routes by mouth [17,18]. Due largely to a desire to reduce side effects associated with sublingual administration, misoprostol is administered buccally (between the gums and cheek) for early medical abortion in a number of Latin American settings [19,20]. Yet there is limited evidence about its efficacy. The few studies that have assessed buccal administration have used different dosing and timing intervals and obtained considerably lower efficacy than what has been documented using vaginal or sublingual regimens [21–23].

Accordingly, we undertook the current study to document the efficacy, safety/side effects and acceptability of buccal administration of the misoprostol-only regimen recommended by WHO and to compare these outcomes to sublingual administration. We hypothesized that sublingual administration would be superior to buccal administration in incidence of continuing pregnancy but inferior in incidence and severity of some side effects.

2. Materials and methods

2.1. Study design and randomization

We conducted this multicenter, randomized trial between April 2015 and September 2016 at six health clinics located in urban and periurban settings of two Latin American countries. All study sites were providing medical abortion or about to begin provision prior to study startup. We obtained central approval from the Allendale Investigational Review Board for all study centers. We included women seeking abortion with pregnancy duration ≤10 weeks. Investigators verified pregnancy by ultrasonography, urine testing or both, and ascertained gestational age by the woman's report of her last menstrual period plus vaginal ultrasound measurements or a bimanual exam. We excluded women with contraindications to misoprostol (intrauterine device in place or history of allergies to prostaglandins), confirmed or suspected ectopic or molar pregnancy, and anyone not willing to provide contact information and return for follow-up.

Gynuity Health Projects in New York carried out computer-generated randomization that was stratified by site with a block size of 10. We masked allocation using sealed, consecutively numbered opaque envelopes, each containing a card revealing the participant's study group allocation (sublingual or buccal misoprostol). Investigators at each clinic distributed study packets labeled with a unique identification number and containing group allocation envelopes in sequential order as participants enrolled. To blind study staff, providers and participants were instructed not to ask about or reveal group allocation until the participant's exit interview.

2.2. Procedures

After confirming eligibility and obtaining consent, trained study staff gave participants a multilevel urine pregnancy test (MLPT) and instructions for use to obtain a baseline human chorionic gonadotropin (hCG) level [24]. Participants also received a study packet containing the following: their study group allocation along with written and pictorial instructions for administering the misoprostol; three sealed envelopes with four misoprostol 200-mcg tablets; one sealed envelope with nine ibuprofen 600-mg tablets; one MLPT; and a study card containing instructions for administering the ibuprofen and MLPT and space for recording details about administration of misoprostol, ibuprofen and MLPT. We included MLPTs to assess their effectiveness and acceptability for home follow-up as a secondary study aim not intended to replace standard follow-up at each site; we plan to report these findings separately.

The study regimen consisted of three doses of misoprostol 800 mcg in blister packs and administered every 3 h per the assigned study group. Participants used the first dose at the clinic or a location of their choice; if used at the clinic, study staff left the room to preserve blinding. Participants used the remaining doses at a location of their choice, typically their home. Study staff encouraged participants to take one ibuprofen 600 mg for pain as needed every 8 h and to use the MLPT 1 week after misoprostol administration to ascertain their follow-up hCG level. Staff instructed participants to call the clinic with any questions or concerns, and to return at any point if they experienced heavy or persistent bleeding or desired surgical completion.

Participants attended follow-up visits between 7 and 14 days after misoprostol administration, at which study staff assessed abortion status by vaginal ultrasonography, pregnancy test or physical exam per standard clinic procedures. If providers diagnosed continuing pregnancy, they were to offer immediate aspiration. For incomplete abortion, providers offered the option of immediate aspiration or waiting 1 more week, with or without additional misoprostol 800 mcg, to be administered per the participant's study group allocation. If a participant elected additional misoprostol and/or waiting 1 more week, a second follow-up visit was scheduled 7 days later. At the final follow-up visit, study staff asked all participants about their abortion experiences and misoprostol administration (including route used). If a woman did not return for her scheduled follow-up visit, study staff made up to three attempts to contact her, after which she was considered lost to follow-up. The trial ended after meeting the enrollment goal.

2.3. Outcomes and analysis

We assessed abortion outcomes at initial and final follow-up using the last attended follow-up as the final visit. The primary outcome was continuing pregnancy at initial follow-up (defined as fetal cardiac activity on ultrasonography or absent bleeding combined with other symptoms of continuing pregnancy). Secondary outcomes included continuing pregnancy at final follow-up, successful abortion at initial and final follow-up (defined as complete uterine evacuation without aspiration), incomplete abortion at initial and final follow-up (defined as persistent non-viable pregnancy or gestational sac), self-reported side effects, acceptability of the abortion procedure and complications.

We expected lower continuing pregnancy rates with sublingual administration, so we estimated sample size using a one-sided test based on an expected rates of 6% with sublingual administration [16] and 14% with buccal administration [23].We estimated a sample size of 346 (173 per group) using an alpha=0.05 and power=0.80; we increased the minimum enrollment to 382 women (191 per group) to account for a possible 10% loss to follow-up rate.

We calculated the proportion of women with complete abortion, incomplete abortion and continuing pregnancy at initial and final follow-up. We analyzed all outcomes as intention-to-treat. We used χ^2 and Fisher's Exact Tests to assess group differences in outcomes, side effects and acceptability measures. We also assessed differences in outcomes by gestational age. We conducted data analyses using Stata SE, version 15.1, and considered p values <.05 as significant.

3. Results

Of the 597 women screened, we enrolled 401 women, randomizing 202 to misoprostol buccally and 199 to misoprostol sublingually (Fig. 1). We excluded three women after enrollment because they did not meet eligibility criteria: one had a pregnancy of 86 days' gestation; another had a tongue defect that prevented her from being administered pills sublingually; and a third was seeking care for a failed medical abortion. Ten women were lost to follow-up; their gestational ages were ≤49 days (2/10), 50–56 days (1/10), 57–63 days (5/10) and 64–70 days (2/10). Participant characteristics are presented in Table 1.

Table 2 presents abortion status at initial and final follow-up. The randomization groups had similar time between enrollment and initial follow-up (mean of 9.5 days in the buccal arm and 9.7 days in the sublingual arm). Women experienced higher rates of continuing pregnancy at initial follow-up after buccal (5.5%) than after sublingual (1.1%)

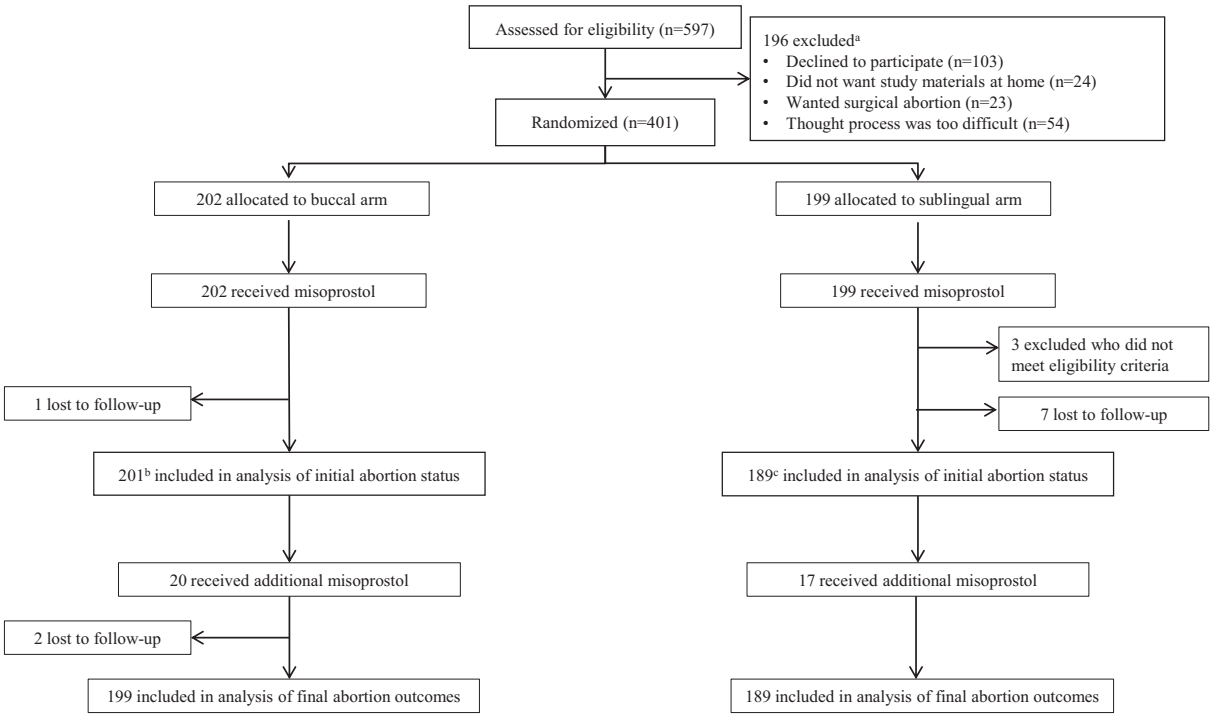

Fig. 1. Consort flowchart. [a]Study personnel could select more than one reason. [b]One phone follow-up. [c]Two phone follow-ups.

administration (p=.02). While the study protocol specified that women with continuing pregnancy should be offered immediate vacuum aspiration, most providers offered a choice of aspiration or additional misoprostol plus waiting 1 more week. Among those diagnosed with continuing pregnancy, 9/13 (69%) received additional misoprostol; five received one additional dose of 800 mcg, and four (two per study arm) received three additional doses of 800 mcg (Fig. 2). This treatment resulted in successful resolution of 5/7 (71%) cases in the buccal arm and 1/2 (50%) in the sublingual arm. Final continuing pregnancy rates were 5/198 (2.5%) in the buccal arm and 1/186 (0.5%) in the sublingual arm (p=.22). At the initial follow-up visit, 190/386 (50%) of all participants underwent ultrasonography compared with 10/13 (77%) of those diagnosed with continuing pregnancy and 32/38 (84%) of those diagnosed with incomplete abortion.

Table 1
Characteristics of women having a medical abortion with buccal or sublingual misoprostol alone in two Latin American countries

	Buccal (*n*=202)	Sublingual (*n*=196)
Country of residence		
Country A	124 (61.4)	123 (62.8)
Country B	78 (38.6)	73 (37.2)
Education		
None	1 (0.5)	1 (0.5)
Primary	34 (16.8)	36 (18.4)
Secondary	102 (50.5)	104 (53.1)
University or higher	64 (31.7)	54 (27.6)
Missing data	1 (0.5)	1 (0.5)
Currently married or cohabitating		
Yes	127 (62.9)	117 (59.7)
No	74 (36.6)	77 (39.3)
Missing data	1 (0.5)	2 (1.0)
Age (years)	27.2±7.0	26.9±7.3
Parity		
Nulliparous	59 (29.2)	54 (27.6)
Parous	143 (70.8)	142 (72.5)
Prior abortion		
Yes	58 (28.7)	45 (23.0)
No	144 (71.3)	150 (76.5)
Missing data	0 (0.0)	1 (0.5)
Gestational age in days		
≤49	130 (64.4)	119 (60.7)
50–56	37 (18.3)	30 (15.3)
57–63	21 (10.4)	28 (14.3)
64–70	14 (6.9)	18 (9.2)
Missing data	0 (0.0)	1 (0.5)
Means of pregnancy verification		
Pregnancy test only	81 (40.1)	78 (39.8)
Ultrasound only	13 (6.4)	21 (10.7)
Pregnancy test + ultrasound	108 (53.5)	96 (49.0)
Missing data	0 (0.0)	1 (0.5)

All data are presented as *n* (%) or mean ± standard deviation.

Table 2
Abortion status and final outcomes of women having a medical abortion with buccal or sublingual misoprostol alone in two Latin American countries

	Buccal	Sublingual	p value
Status at initial follow-up (7–14 days after misoprostol)	*n=201*	*n=189*	.03
Success	170 (84.6)	165 (87.3)	
Incomplete abortion	18 (9.0)	22 (11.6)	
Continuing pregnancy	11 (5.5)	2 (1.1)	
Uncertain	2 (1.0)	0 (0.0)	
Final outcome (status at final follow-up)[a]	*n=199*	*n=189*	.65
Success	184 (92.5)	177 (93.7)	
Surgical intervention	15 (7.5)	12 (6.4)	
Reason for surgical intervention	*n=15*	*n=12*	-
Continuing pregnancy	5	1	
Persistent nonviable pregnancy or sac	4	10	
Substantial debris in uterus	4	0	
Excessive bleeding	1	0	
Requested by woman	1	0	
Unknown/other	0	1	

Data are presented as *n* (%).
Note: Analysis of differences in continuing pregnancy rates by study group yields p=.02 at initial follow-up and p=.22 at final follow-up.
[a] Final outcome refers to abortion status at the woman's last follow-up visit. If she had only one follow-up visit, her status at initial follow-up and her final outcome were the same; if she had a second follow-up visit, the final outcome was recorded at the time of the second visit.

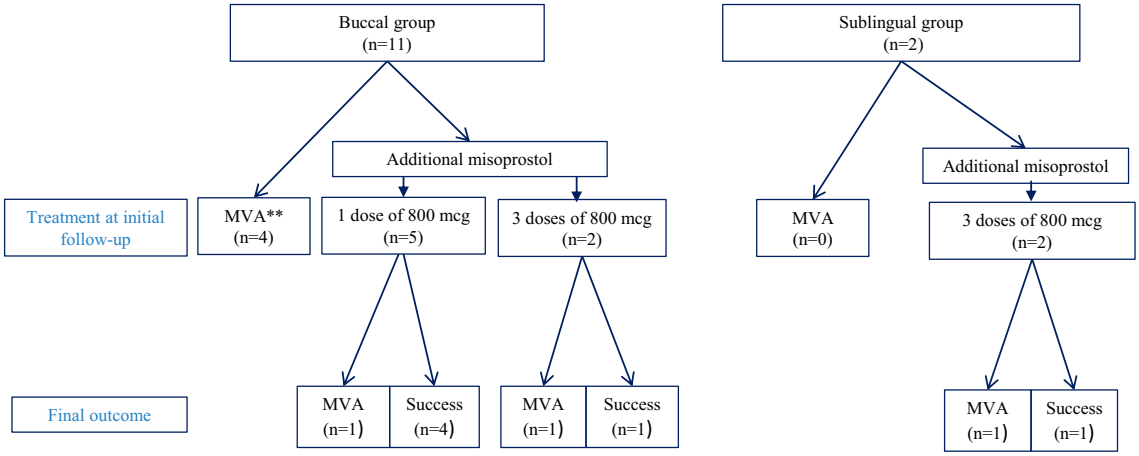

Fig. 2. Management of continuing pregnancies among women receiving early pregnancy termination with buccal or sublingual misoprostol alone. * Treatment of continuing pregnancies reflected local practices at each study site. ** MVA denotes manual vacuum aspiration.

Providers diagnosed 40 women with incomplete abortion at initial follow-up, 29 (73%) of whom received one additional dose of misoprostol 800 mcg. One serious adverse event occurred involving a woman who went to her local hospital for excessive bleeding and underwent a surgical evacuation with overnight stay per hospital policy. She had no other complications. Two women in the buccal arm were initially classified as uncertain abortion outcome since, in both cases, ultrasound was not used and study providers were unsure whether they had continuing pregnancy or incomplete abortion. Overall success rates increased from 70/201 (84.6%) to 184/189 (92.5%) in the buccal arm and 165/189 (87.3%) to 177/189 (93.7%) in the sublingual arm with additional misoprostol plus waiting time. Of note, gestational age had no impact on abortion outcomes at initial or final follow-up (Table 3).

Self-reported side effects were similar in the randomization groups with exception of chills and fever which were both more common in the sublingual arm (Table 4). Overall satisfaction was high in both groups, although it was slightly higher in the sublingual arm (Table 5). Satisfaction was lowest among those who received surgical aspiration: 52% were unsatisfied or very unsatisfied, as compared with only 1% of those with successful outcomes. While acceptability of side effects and pain was considerably lower than overall satisfaction, most women (85%–90%) in both groups reported that they would choose medical abortion if needed in the future.

Table 3
Abortion status and final outcomes by gestational age group among women having a medical abortion with buccal or sublingual misoprostol alone in two Latin American countries.

	<49 days	50–56 days	57–63 days	64–70 days	p value
Status at initial follow-up					
Buccal arm	*n=130*	*n=37*	*n=20*	*n=14*	.33
Success	109 (83.9)	33 (89.2)	19 (95.0)	9 (64.3)	
Incomplete abortion	12 (9.2)	2 (5.4)	0 (0.0)	4 (28.6)	
Continuing pregnancy	7 (5.4)	2 (5.4)	1 (5.0)	1 (7.1)	
Uncertain	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Sublingual arm	*n=118*	*n=29*	*n=24*	*n=17*	.15
Success	99 (83.9)	28 (96.6)	21 (87.5)	16 (94.1)	
Incomplete abortion	18 (15.3)	1 (3.5)	3 (12.5)	0 (0.0)	
Continuing pregnancy	1 (0.9)	0 (0.0)	0 (0.0)	1 (5.9)	
Final outcome					
Buccal arm	*n=129*	*n=37*	*n=20*	*n=13*	.57
Success	119 (92.3)	33 (89.2)	20 (100.0)	12 (92.3)	
Surgical intervention	10 (7.8)	4 (10.8)	0 (0.0)	1 (7.7)	
Sublingual arm	*n=118*	*n=29*	*n=23*	*n=17*	.24
Success	107 (90.7)	29 (100.0)	23 (95.8)	17 (100.0)	
Surgical intervention	11 (9.3)	0 (0.0)	1 (4.2)	0 (0.0)	

All data are presented as *n* (%).

4. Discussion

Our findings suggest that sublingual administration is superior to buccal administration in reducing continuing pregnancy risk after a three-dose regimen of 800 mcg misoprostol. Although group differences were only statistically significant at initial follow-up, their relative magnitude was consistent at both follow-up points, with rates of continuing pregnancy about five times as high in the buccal arm as compared with the sublingual arm. Pharmacokinetic properties that differ by route may explain these results. In particular, sublingual administration is associated with a quicker onset of action, higher peak plasma concentration and greater bioavailability than the buccal route [25–28], indicating that sublingual administration may have a greater impact on uterine contractility than buccal administration.

Nevertheless, continuing pregnancy in both groups was consistently lower than expected. At initial follow-up, the rate of 1% in the sublingual arm was considerably lower than the 6% rate reported by von Hertzen and colleagues [16] after using the same regimen and route. Final

Table 4
Self-reported side effects among women having a medical abortion with buccal or sublingual misoprostol alone in two Latin American countries

	Buccal (n=197)	Sublingual (n=186)	p value
Diarrhea			.20
None	65 (33.0)	52 (28.0)	
Mild	54 (27.4)	48 (25.8)	
Moderate	58 (29.4)	73 (39.3)	
Severe	20 (10.2)	13 (7.0)	
Nausea			.97
None	116 (58.9)	107 (57.5)	
Mild	45 (22.8)	46 (24.7)	
Moderate	34 (17.3)	31 (16.7)	
Severe	2 (1.0)	2 (1.1)	
Vomiting			.45
None	160 (81.2)	146 (78.5)	
Mild	25 (12.7)	21 (11.3)	
Moderate	10 (5.1)	17 (9.1)	
Severe	2 (1.0)	2 (1.1)	
Fever			.01
None	86 (43.7)	68 (36.6)	
Mild	39 (19.8)	36 (19.4)	
Moderate	71 (36.0)	70 (37.6)	
Severe	1 (0.5)	12 (6.5)	
Chills			.00
None	36 (18.3)	19 (10.2)	
Mild	43 (21.8)	34 (18.3)	
Moderate	111 (56.4)	109 (58.6)	
Severe	7 (3.6)	24 (12.9)	

All data are presented as *n* (%).

Table 5
Satisfaction and acceptability among women having a medical abortion with buccal or sublingual misoprostol alone in two Latin American countries

	Buccal	Sublingual	p value
Satisfaction with procedure	*n=197*	*n=186*	.41
Very Satisfied or satisfied	155 (78.7)	156 (83.9)	
Neutral	32 (16.2)	22 (11.8)	
Unsatisfied or very unsatisfied	10 (5.1)	8 (4.3)	
Acceptability of side effects	*n=198*	*n=186*	.86
Very acceptable or acceptable	126 (63.6)	119 (64.0)	
Neutral	66 (33.3)	63 (33.9)	
Unacceptable or very unacceptable	6 (3.0)	4 (2.2)	
Acceptability of pain	*n=198*	*n=186*	.30
Very acceptable or acceptable	122 (61.6)	106 (57.0)	
Neutral	64 (32.3)	61 (32.8)	
Unacceptable or very unacceptable	12 (6.1)	19 (10.2)	
Would choose medical abortion for a future procedure	*n=196*	*n=184*	.23
Yes	166 (84.7)	164 (89.1)	
No	20 (10.2)	10 (5.4)	
Not sure	10 (5.1)	10 (5.4)	

All data are presented as *n* (%).

rates were even lower in both groups (0.5% in the sublingual arm and 2.5% in the buccal arm). While we are not sure what accounts for these differences, one possible factor is increased provider comfort with misoprostol for early medical abortion and willingness to offer both additional misoprostol and waiting time at follow-up in lieu of resorting to immediate surgical intervention. Decreased use of ultrasound may also have prevented misuse of ultrasound results to justify intervention.

In both groups, the rates of successful, complete abortion were comparable, and provision of additional misoprostol plus waiting time yielded an absolute increase of 6%–8% in overall success. This finding supports the recent WHO decision to remove the maximum number of doses from its guidelines for misoprostol-only abortions among pregnancies <12 weeks [29]. Although additional misoprostol is known to treat incomplete abortion, the potential impact on continuing pregnancies has been observed in only a few small studies to date [30,31]. Our findings suggest that additional misoprostol can be successfully used to treat many cases of continuing pregnancy. Unfortunately, these data do not allow us to assess the relative contribution of additional misoprostol versus further waiting time to resolution of continuing pregnancy.

The incidence of self-reported side effects was similar between groups on most measures with the exception of fever and chills, which each occurred with greater frequency in the sublingual arm (in both cases, most differences were in reporting of severe effects). Similar differences have been found in studies of misoprostol for postpartum hemorrhage, which have shown misoprostol's thermoregulatory effects to be more prominent following sublingual administration than for other routes [32]. These findings are also consistent with evidence related to misoprostol use following mifepristone administration [33]. Nevertheless, in both groups, most side effects were mild to moderate and were transient.

Overall, our results were consistent with our research hypothesis, indicating that sublingual administration was superior to buccal administration in incidence of continuing pregnancy but inferior in incidence of fever and chills. In order to determine which route is preferable, consideration of the relative risks and benefits is warranted. In our study, the absolute incidence of fever and chills was 7.1% and 8.1% lower, respectively, while the absolute incidence of continuing pregnancy was 4.4% higher in the buccal arm than in the sublingual arm. For many women, an undiagnosed or untreated continuing pregnancy resulting from a failed misoprostol-only abortion could have dire consequences, particularly in settings with limited access to safe abortion services. In such cases and whenever the primary goal is to avoid continuing pregnancy, sublingual administration of misoprostol 800 mcg every 3 h for three doses should be recommended over buccal administration of this regimen. On the other hand, if there is concern about chills or fever and the woman's primary goal is to avoid surgery, buccal administration may be preferable.

There were some study limitations, including our selection of a one-sided test for assessing the primary outcome. Since the incidence of continuing pregnancy was lower than anticipated, we were underpowered to detect differences. In spite of this, we found that sublingual administration was superior to buccal administration at initial follow-up. We were also unable to ensure that study staff were completely blinded to participants' group allocation or to ensure provider adherence to procedures for management of continuing pregnancy. Yet provision of additional misoprostol for continuing pregnancy reflects current practice in these settings and represents new information with the potential to inform practice. In addition, only a small number of participants had gestations <42 days, so we do not know if our findings can apply to such pregnancies.

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