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CURBSIDE CONSULT

How Effective Is Misoprostol Alone for Medication Abortion?

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Abstract

With recent severe restrictions to abortion accessibility in the United States and a pending Supreme Court case challenging the Food and Drug Administration's approval of mifepristone, evidence-based strategies to protect and expand access to abortion care are needed. Two safe and effective regimens for medication abortion are widely used globally — misoprostol-only and misoprostol in combination with mifepristone. However, misoprostol-only regimens are rarely used in the United States. In 2023, the National Abortion Federation and the Society of Family Planning updated their recommended protocol for misoprostol-only for medication abortion to 800 μg of misoprostol administered buccally, sublingually, or vaginally every 3 hours for three or more doses. To characterize the data supporting this specific regimen, this article reviews the relevant literature to address the question of how effective misoprostol-only is for medication abortion. The authors conclude that the updated misoprostol regimen is highly effective and a potential strategy for expanding access to abortion.

Misoprostol-Only Medication Abortion: A Brief Background

Fifty years ago in 1973, the Searle pharmaceutical company developed misoprostol as a medication for the treatment of gastrointestinal ulcers.[1] By the late 1980s, feminists in Brazil noticed an opportunity in a misoprostol warning label that cautioned about risk of miscarriage, and the drug took off as the first method of medication abortion.[1] Today, two regimens for medication abortion are widely used globally, both featuring misoprostol: misoprostol in combination with mifepristone (the combined regimen) or misoprostol-only.[2] Research on both abortion regimens has consistently demonstrated the high safety and effectiveness of these medications.

In the United States, however, while the combined regimen is commonly offered by clinicians who provide medication abortion, misoprostol-only regimens have rarely been made available to patients.[3] Systematic reviews that include studies with a wide range of

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misoprostol-only regimens (with varying dosage, interval, and route of administration) have estimated that the combined regimen is approximately 95% effective versus 78% for misoprostol-only.[2,4-6] A 2022 Cochrane review assessed randomized, placebo-controlled trials that compared a range of misoprostol-only regimens versus the combined regimen.[6] That review concluded that use of misoprostol-only (in the regimens studied) leads to more diarrhea and may increase the risk of incomplete abortion as compared with the combined regimen; the conclusion was made on the basis of what the review characterized as "low-certainty evidence."[6]

Recent severe restrictions on abortion access in the United States following the *Dobbs v. Jackson Women's Health Organization* decision in June 2022 coupled with a Supreme Court case challenging the Food and Drug Administration (FDA) regulation of mifepristone[7] have strengthened the case for leveraging all evidence-based strategies to protect and expand access to abortion care, including misoprostol-only regimens. In preparation for potential additional restrictions on mifepristone, professional associations and medical groups reviewed the existing evidence and put forward a recommended protocol for the provision of misoprostol-only abortion in the United States. The updated regimen recommended by the National Abortion Federation[8] and the Society of Family Planning[9] is as follows: 800 μg of misoprostol administered buccally, sublingually, or vaginally every 3 hours for three or more doses.

Prior pooled estimates of the effectiveness of misoprostol-only regimens were not determined exclusively on the basis of this newly recommended protocol for a misoprostol-only medication abortion regimen.[9] As clinicians consider offering misoprostol-only regimens, they, their clinic staff, advocates, and the general public need a more accurate estimate of the effectiveness of this specific misoprostol-only regimen. This curbside consult reviews the relevant literature focused on studies that reported on abortion completion outcomes using this specific protocol to answer the following question: How effective is the medication abortion regimen of 800 μg of misoprostol administered buccally, sublingually, or vaginally every 3 hours for three or more doses?

The Literature on Misoprostol-Only Regimens

Researchers have studied and published on a wide range of regimens to establish the dosage and route of administration of misoprostol for abortion. Over the past several decades, researchers have studied regimens that differ widely in dosage (200 to 1200 μg), interval between doses (3 to 48 hours), route of administration (buccal, oral, sublingual, or vaginal), and timing of outcome measurement (<24 hours to 4 weeks).[5,10] The often cited approximately 78% effectiveness of the misoprostol-only regimen comes from a seminal 2019 systematic review that pooled outcomes across all regimens studied in clinical settings.[5,9] Notably, 44% of analyzed participants in that review used a regimen wherein two or three doses of misoprostol were administered vaginally 24 to 48 hours apart[11,12] — a regimen no longer in wide use.[2,9,13] Additionally, only 1 of the 42 included studies in the 2019 review reported on outcomes from the most updated National Abortion Federation– and Society of Family Planning–endorsed misoprostol-only regimen.[9,14]

Since publication of the 2019 systematic review, at least six additional studies[15-20] have been published that disaggregated abortion completion outcomes following use of 800 μg of misoprostol administered buccally, sublingually, or vaginally every 3 hours for at least three doses, in addition to the one trial[14] included in the 2019 systematic review. In 2023, Raymond et al. updated the 2019 systematic review to include five of these six new studies; this review, however, similarly did not report outcomes specific to the National Abortion Federation– and Society of Family Planning–endorsed misoprostol-only regimen. Thus, we provide an assessment of the set of relevant studies to characterize the evidence for the updated misoprostol-only regimen (Table 1). These studies — two randomized trials, three prospective cohort studies, and two retrospective cohort studies — included participants from 13 countries, including a range of low-, middle-, and high-income countries. Five of the seven studies included participants up to 10 weeks of pregnancy, while two included participants with pregnancies through 16 weeks.

In the randomized trials, investigators randomized participants to sublingual versus vaginal administration[14] or sublingual versus buccal administration of misoprostol.[15] Patients took the first dose of misoprostol under clinician supervision, while subsequent doses were taken at home; participants returned 1–2 weeks later for outcome evaluation.[14,15] In one observational study,[19] participants received the pills in the mail or in person after a consultation with a physician, and they took all doses at home. In the remaining four observational studies, participants obtained and took pills outside the formal health system or "self-managed" their abortions, following guidance on the currently endorsed regimen from trained abortion accompaniment counselors,[16,18] a community

Table 1. Data Extracted from Two Randomized Trials and Five Observational Studies That Reported Abortion Completion Outcomes Following Use of the Misoprostol-Only Regimen of 800 μg of Misoprostol Administered Buccally, Sublingually, or Vaginally Every 3 Hours for Three or More Doses.*

Study	Gestational Limit, Weeks	Enrolled	Confirmed Use of Miso	Analyzed	Complete Abortion without Procedural Intervention	Complete without Procedural Intervention, %	Continuing Pregnancies	No. Lost to Follow-up among Confirmed Miso Users	Lost to Follow-up among Confirmed Miso Users, %	Dosage Miso, μg	No. of Doses	Hours between Doses	Route of Administration	Timing of Completion Assessment, Weeks
Randomized clinical trials														
von Hertzen et al. 2007[14] — vaginal arm	9	516	516	513	434	84.6	20 (3.9%)	3	0.6	800	3	3	V	2
von Hertzen et al. 2007[14] — sublingual arm	9	517	517	512	431	84.2	29 (5.7%)	5	1.0	800	3	3	SL	2
Sheldon et al. 2019[15] — buccal arm	10	202	202	199	184	92.5	5 (2.5%)	3	1.5	800	3+	3	B	1–2
Sheldon et al. 2019[15] — sublingual arm	10	199	199	189	177	93.7	1 (0.5%)	10	5.0	800	3+	3	SL	1–2
Prospective observational studies														
Moseson et al. 2020[16]	16	227†	94	94	87	92.6	Not reported	0	0.0	800	3+	3	SL	3
Foster et al. 2022[17]	10	120	120	120	120	100.0	0 (0%)	0	0.0	800	3	3	SL	4
Jayaweera et al. 2023[18]	16	1352†	637	532‡	529	99.4	Not reported	0	0.0	800	3+	3	SL	3
Retrospective records reviews														
Raymond et al. 2023[19]	10	911	567	476	389	81.7	45 (9.4%)	91	10§	800	3+	3	B, SL, V	4
Johnson et al. 2023[20]	10	1016	568	568	498	87.7	Not reported	0	0§	800	3	3	SL	4

* Routes of administration are buccal (B), sublingual (SL), and vaginal (V). Miso denotes misoprostol.

† As these studies were observational, the studies enrolled people prior to participants confirming a plan to self-manage and prior to their obtaining or taking the pills. Thus, the total number enrolled is higher than the number who were confirmed to obtain and use misoprostol-only. The rest of those enrolled used mifepristone plus misoprostol (Moseson et al.,[16] n=107; Jayaweera et al.,[18] n=610) or a different misoprostol-only regimen, obtained abortion care elsewhere, decided not to take the pills, or were lost to follow-up prior to confirming use of pills.

‡ Of the 637 participants confirmed to take misoprostol, n=105 used fewer than three doses of misoprostol; we report here only those outcomes among those who reported using the National Abortion Federation– and Society of Family Planning–endorsed regimen of three or more doses of 800 μg misoprostol every 3 hours.

§ For these retrospective studies, loss to follow-up among confirmed users of misoprostol was 10% in the study by Raymond et al.[19] and 0% in the study by Johnson et al.[20] However, loss to follow-up among potential users of misoprostol in these two studies was much higher: 52.2% in the study by Raymond et al.[19] and 55.9% in the study by Johnson et al.[20]

health worker,[17] or an online telehealth provider.[20] Researchers in all observational studies ascertained outcomes through last participant self-report later than was done for the randomized trials, at 3 to 4 weeks after taking the pills, compared with follow-up at 1 to 2 weeks in the randomized trials.

Abortion completion without procedural intervention following use of three or more doses of 800 μg of misoprostol every 3 hours ranged from 82 to 100% across the seven studies (Fig. 1). Two studies quantitatively assessed the risk of bias due to loss to follow-up and self-report of the outcome through multiple imputation[19] or Monte Carlo sensitivity analysis,[18] and they found bias-corrected estimates ranging from 81 to 95%. Still, limitations of the included retrospective observational studies include high loss to follow-up. Johnson et al.[20] reached only 568 of 1016 individuals, and Raymond et al.[19] had outcomes for only 476 of 911 individuals. A limitation of retrospective reviews is the inability to conduct concurrent follow-up; depending on if or how outcomes differed among participants with missing data, the true effectiveness of the misoprostol-only regimen could vary.

An additional outcome of interest is continuing pregnancy. The two randomized trials measured continuing pregnancy, which they defined as growing gestational sac with fetal heart activity or absent bleeding combined with other symptoms of continuing pregnancy.[14,15] One retrospective cohort study[19] defined continuing pregnancy as any post-treatment ultrasound showing fetal cardiac activity, fetal growth, or a gestational age without mention of the absence of fetal cardiac activity or if the patient reported that another provider diagnosed a healthy pregnancy. Across included studies, 0 to 9% of individuals had a continuing pregnancy at 2 to 4 weeks postabortion (Fig. 2 and Table 1). The studies of self-managed abortion did not measure continuing pregnancy as distinct from other forms of failing to have a complete abortion, such as incomplete abortion or positive pregnancy test.

Implications for Clinical Care

All seven identified studies that examined the updated misoprostol-only regimen reported higher effectiveness than the 78% that is routinely cited in the scientific and clinical

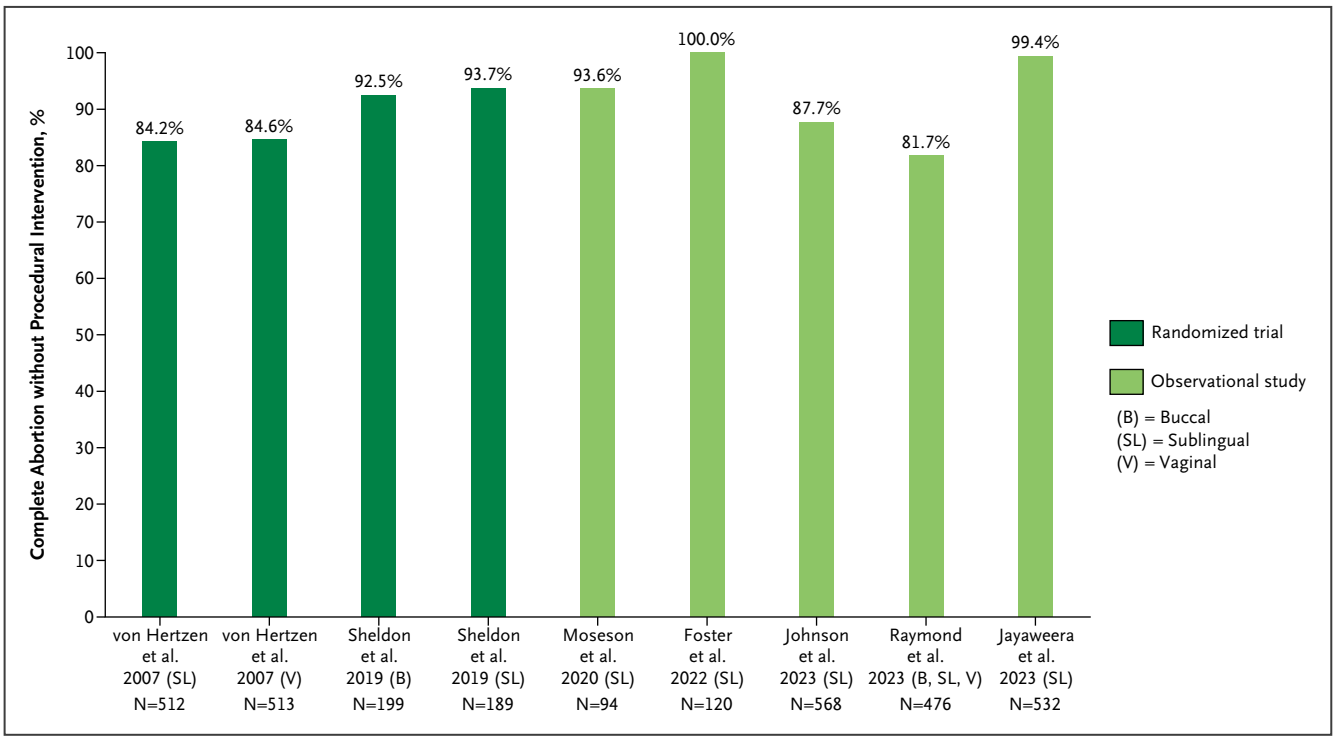

Figure 1. Abortion Completion without Procedural Intervention Following Use of 800 μg of Misoprostol Every 3 Hours for Three or More Doses by Route of Administration.

Data were extracted from two randomized controlled trials and five observational studies that reported outcomes following use of this regimen.

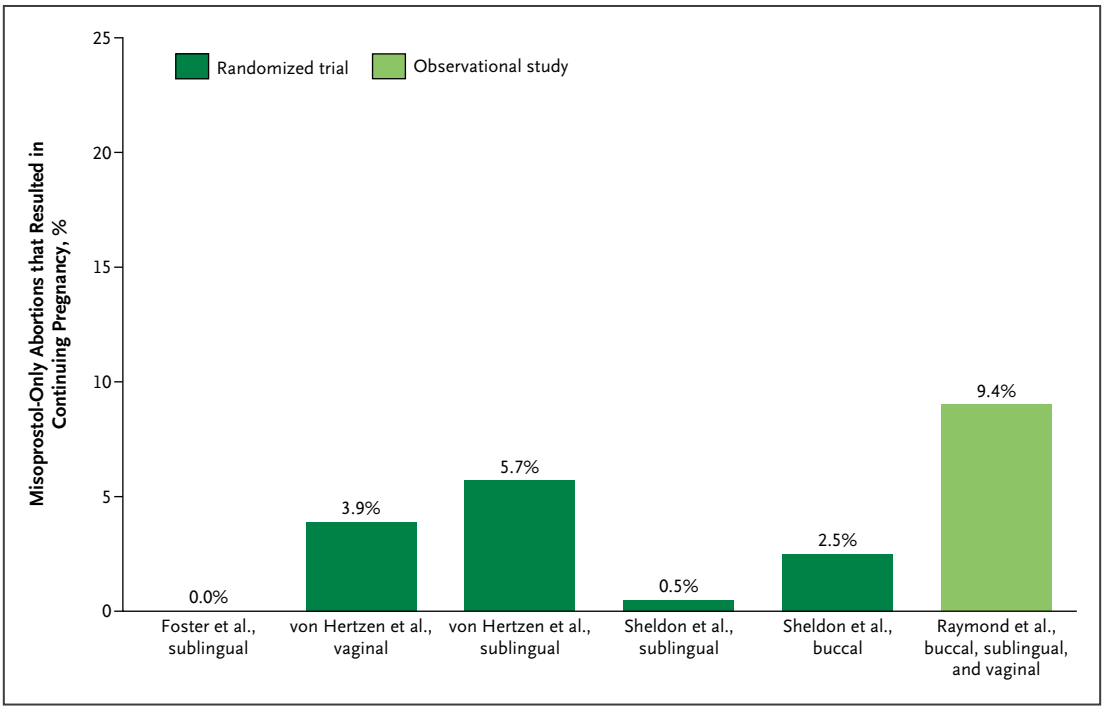

Figure 2. Continuing Pregnancies Detected Approximately 2 to 4 Weeks after Use of 800 μg of Misoprostol Every 3 Hours for Three or More Doses by Route of Administration across Six Study Groups of Two Randomized Trials and Two Observational Studies.

literature, an estimate from a pooled meta-analysis that includes studies using various doses, routes, and dosing intervals.[5] However, the variation in observed effectiveness across these seven studies — from 82 to 100% — merits discussion. First, the study designs may have driven some of the observed differences. For trials in which clinicians evaluated abortion completion (completion range: 82 to 94%), the assessment occurred 1 to 2 weeks earlier than in the studies in which participants self-managed abortion (completion range: 88 to 100%); abortions categorized as "incomplete" at 1 to 2 weeks might have resulted in a complete abortion with additional time.[21,22] Second, one of the randomized trials capped misoprostol doses at three doses, while the studies in self-managed settings allowed additional doses in the relatively rare event that they were needed. Third, the randomized trials primarily relied on ultrasonography to ascertain abortion completion, while the self-managed studies relied on participant self-assessment. While more than half of the participants in the studies of misoprostol-only use in self-managed settings received ultrasound confirmation of abortion completion or used a pregnancy test to confirm completion, not all did so. Research has demonstrated that self-assessment of medication abortion outcome at home through a home pregnancy test and symptoms checklist or a pictorial chart is noninferior to clinical assessment through 9 weeks of pregnancy[23] and additionally, that people can accurately assess whether they have expelled the gestational sac.[24] The approach to self-assessment of abortion completion in self-managed settings has diverged slightly from approaches in randomized trials — often forgoing a shorter checklist in order to gather additional information on symptoms, experience, and information provided by trained accompaniers, especially where pregnancy tests may be less accessible. Studies of self-managed abortion have also reported on outcomes later in pregnancy than the included randomized trials, and completion may be easier to evaluate given the larger mass of pregnancy tissue and thus, greater ease of visually confirming expulsion of the fetus.[25] In self-managed and retrospective studies where neither ultrasound or pregnancy tests were utilized, it is possible that some treatment failures were missed. Just as in randomized trials where ultrasound was utilized, it is possible that some abortions classified as treatment failures might have resulted in a complete abortion without the need for procedural intervention with additional time or additional doses.[21,22]

Beyond differences in study design, there is another core contextual difference across studies. Due to legality, safety, cost, privacy, stigma, and other concerns, people who self-manage their abortions in the contexts where researchers have studied misoprostol-only often have less access to or are less inclined to interact with clinical settings compared with participants in a randomized clinical trial who are required to return to the clinic at 1 to 2 weeks, at which point they are routinely offered an aspiration or other procedure to complete the abortion if desired. Participants in studies of self-managed use, however, are not routinely offered intervention on that timeline. Particularly in studies where participants were accompanied by community counselors or health workers (completion range: 93 to 100%), one possible factor is increased comfort with misoprostol for early medication abortion and willingness to offer both additional misoprostol and waiting time at follow-up in lieu of resorting to immediate procedural intervention — counseling in an expectant management approach versus default to intervention. As such, some element of measured effectiveness observed in the research on misoprostol-only may have to do with whether people are encouraged or required to seek clinical care as well as their comfort with and ability to access that care.

Moving Forward

This discussion of the scientific evidence on effectiveness of the updated regimen for misoprostol-only medication abortion suggests that this regimen is highly effective (82 to 100%). As this range includes a lower bound that is below the estimated effectiveness of the combined regimen (approximately 95%),[6] people seeking abortions should be informed of these differences and work with their provider to make a plan for care seeking in the event of failure of either regimen.

It is equally critical to acknowledge that effectiveness is not the only consideration for people seeking abortion care; cost, accessibility, timeliness, feelings of preparedness, and provider trust as well as pain and symptom management contribute to method choice and assessment of quality. Misoprostol-only is a method that, as for many around the globe, may be the right choice for some people seeking abortion in the United States. In the future, misoprostol-only medication abortion could be more accessible in the United States than the combined regimen given that misoprostol is not restricted by the FDA Risk Evaluation and Mitigation Strategy and could be offered by wider numbers and cadres of providers. Misoprostol is less costly and initiates an abortion process more quickly than the combined regimen (which rather than starting right away, requires waiting 24 to 48 hours after ingesting mifepristone). Ample research has demonstrated that nonclinically trained providers can support people to have safe, effective, supported, and highly acceptable medication abortions, including misoprostol-only abortions.[2,18,26-28] The public health imperative calls for leveraging all evidence-based interventions to expand access to abortion where possible, and in the rapidly changing abortion landscape in the United States, misoprostol-only medication abortions may play a key role.

Disclosures

Author disclosures are available at evidence.nejm.org.

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