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Special Article

Medication abortion with misoprostol-only: A sample protocol☆,☆☆

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1. Introduction

Mifepristone approval by the United States (U.S.) Food and Drug Administration in 2000 revolutionized abortion care in this country. In 2020, 53% of people having facility-based abortions in the U.S. had medication abortions with mifepristone and misoprostol rather than uterine evacuation procedures [1]. A key advantage of medication abortion is that it can be provided entirely remotely by telemedicine and mail, which has been critical for patients who face barriers to accessing in-person services [2].

In the aftermath of the U.S. Supreme Court's decision in *Dobbs v. Jackson Women's Health Organization* which eliminated federal constitutional protections for abortion, the accessibility and availability of mifepristone are under increasing threat. Medication abortion regimens that do not include mifepristone are therefore of urgent interest. The most studied such regimens use misoprostol either alone or in conjunction with methotrexate or letrozole [3]. Although randomized trials demonstrate that misoprostol-only regimens are somewhat less effective than those that include both mifepristone and misoprostol [4–7], they cause abortion in the large majority of users. Neither methotrexate-misoprostol [8–11] nor letrozole-misoprostol [12–15] regimens have demonstrated advantages in effectiveness, ease of use, or time to abortion over multi-dose misoprostol-only regimens.

In settings where mifepristone is not available, and especially outside the U.S., clinicians and people who self-manage abortion have been using misoprostol-only for decades [16]. Misoprostol-only regimens are endorsed as a medically acceptable option by the

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World Health Organization [17] and other international and national professional guidelines for abortion care [18–20]. However, documented experience in the U.S. has been limited. Here, we present a brief summary of data on misoprostol-only abortion and a sample protocol for U.S. clinicians who wish to offer it.

2. Data on effectiveness and safety of misoprostol-only regimens

A systematic review published in 2019 [21] summarized 38 studies of the effectiveness and safety of a large variety of misoprostol-only regimens for medication abortion in the first trimester. Of the 12,829 patients who provided outcome data, 78% aborted completely without a procedure or unplanned additional medications, a substantially lower proportion than the approximately 95% expected after the use of mifepristone and misoprostol at ≤10 weeks of gestation [22,23]. Several features of misoprostol-only regimens were associated with higher effectiveness, including the number of misoprostol doses, the amount of misoprostol per dose, and administration by a sublingual, vaginal or buccal route (as opposed to orally). The overall data suggested that if vaginal administration is chosen, moistening the misoprostol tablets before insertion may improve effectiveness. One randomized trial reported higher effectiveness after sublingual than buccal administration [24].

The systematic review examined effectiveness among subgroups of patients who received regimens with characteristics associated with higher effectiveness. In the 20 studies in which patients received at least 3 or more doses of misoprostol, the first of which contained 800 μg administered sublingually, vaginally (moistened), or buccally, 87% of the 5338 evaluable patients aborted completely without additional treatment [21]. In three of those studies [25–27], patients took up to four or six doses and had routine clinical follow-up; of the 775 patients in those studies plus 388 patients meeting those criteria in an additional study published since the review [24], the planned treatment was successful in 93%.

Ongoing pregnancy is more likely after the misoprostol-only regimen than after mifepristone and misoprostol. Of all 6359 patients in the 2019 review who were evaluated for ongoing pregnancy after misoprostol-only treatment, 6% had confirmed viable pregnancies at some point during follow-up [21]. This proportion was 3% among patients who took up to 4 to 6 misoprostol doses as described above. Ongoing pregnancies comprised 39% of total treatment failures in the total 6359 patients and 40% in the group who took up to 4 to 6 doses. In contrast, the expected ongoing pregnancy rate after the use of mifepristone and misoprostol through 9 weeks of gestation is about 1% to 2% and about 25% of total treatment failures are ongoing pregnancies [23].

Some studies reported that the effectiveness of the misoprostol-only treatment declined with gestational duration within the first trimester [6,28–30], whereas others did not observe this trend [24–27]. Data on misoprostol-only abortions at 10 to 12 weeks of gestation are limited [21]. No information is available on the use of misoprostol-only when the gestation is so early that the pregnancy cannot be seen on ultrasound. However, some studies have suggested that treatment with mifepristone and misoprostol is less effective in such very early pregnancies than later in gestation [31–34], and it is possible that the same is true of misoprostol-only regimens.

Several recent studies evaluated the effectiveness of misoprostol-only regimens for self-managed abortion outside the U.S. These studies reported very high success; the combined proportion in three such studies was 98% [35–37]. Abortion practice in these settings differed from U.S. practice; most notably, outcome ascertainment relied solely on patient report 3 to 4 weeks after treatment, and procedural intervention was not readily accessible. Thus, US clinicians using this protocol and their patients are unlikely to observe such high effectiveness. Nevertheless, the results of these studies lend insight into experience with and the acceptability of misoprostol-only regimens, particularly in less medicalized settings.

Misoprostol-only treatments are very safe: across all studies in the 2019 review, at most 0.7% of patients were hospitalized or received a transfusion. Bleeding after misoprostol-only typically lasts about 2 weeks [5,38,39]. Some data from studies directly comparing misoprostol-only regimens to those containing mifepristone suggest that the former may result in a higher incidence of side effects, particularly diarrhea, fever, and chills [4,6,39,40]. Two randomized trials suggested that sublingual use may result in more side effects than buccal [24] or vaginal [29] use.

In the 2019 review, 2961 patients provided data on satisfaction, of whom 78% were satisfied or very satisfied, and 76% said that they would use the method again if needed.

3. Sample protocol

The sample protocol (Fig. 1) is intended as a guidance to assist facility-based providers who are familiar with mifepristone and misoprostol use in early pregnancy. Providers should use judgment to adapt the protocol for their practice settings and patient populations. Below are some comments on various provisions of this protocol.

3.1. Patient selection

The sample protocol specifies a gestational limit of 12 weeks, consistent with the 2022 World Health Organization guideline [17]. Otherwise, eligibility criteria are the same as those commonly accepted for medication abortion with mifepristone and misoprostol, except that criteria that apply solely to mifepristone are omitted. Specifically, people who have chronic adrenal failure, inherited porphyria, or allergy to mifepristone, and those who are taking long-term systemic corticosteroids, need not be excluded from receiving misoprostol-only. Pregnancy should be confirmed by urine pregnancy test or ultrasound, and gestational duration assessed by menstrual or other history, examination, or ultrasound [41,42]. Clinicians may choose to consider patient reports of results of these tests as acceptable. Patients with ultrasound-diagnosed pregnancy of unknown location and without signs or symptoms of ectopic pregnancy should be treated according to standard protocols for such cases [19].

3.2. Rh typing and other pretreatment laboratory testing

Rh testing and provision of Rh immune globulin are unnecessary prior to medication abortion before 12 weeks of gestation [43,44], and some recent U.S. [45] and international guidelines [17,20] have been updated to reflect this. Hemoglobin or hematocrit testing is not needed if the patient has no history or symptoms of anemia. If follow-up with serial serum human chorionic gonadotropin (HCG) tests is planned, the patient should provide a serum sample on the day of treatment initiation as a baseline.

3.3. Treatment regimen

The treatment regimen in the sample protocol is flexible, recognizing the many different circumstances in which misoprostol-only may be provided, including in person and via telehealth, as well as variations in patients' ability to obtain additional misoprostol or other abortion treatments if needed after the initial prescription. Thus, the protocol specifies that each patient should receive three or four doses of misoprostol 800 μg at the clinician's discretion, plus an additional dose for use in case of need. The patient should be instructed to take the initial three or four doses at 3 hours intervals regardless of bleeding or other symptoms that occur during use. If

PURPOSE

To enable safe and effective provision of medication abortion with misoprostol-only

ELIGIBILITY CRITERIA

- Pregnancy confirmed by urine or serum test or ultrasound, per documentation or patient report
- Gestational duration ≤12 weeks as determined by menstrual or other history, ultrasound, or pelvic examination
- None of the following symptoms of or risk factors for ectopic pregnancy (unless intrauterine pregnancy has been confirmed):
    - Vaginal bleeding or spotting within the past week
    - Unilateral pelvic pain or significant bilateral pelvic pain within the past week
    - Prior ectopic pregnancy
    - Prior tubal surgery, including permanent contraceptive procedure
    - Intrauterine device in uterus at conception or currently
- No history of hemorrhagic disorder or concurrent anticoagulant therapy
- No history of allergy to misoprostol or other prostaglandin
- Patient has made an informed decision to use misoprostol-only for abortion

TREATMENT

Provide the following:

- Misoprostol 800 mcg x 3-4 doses, per clinician judgment taking into account the patient's specific situation. An additional dose should be provided that the patient can use if needed.
- Analgesics, antipyretic, antiemetics and antidiarrheals as indicated.
- Patient instruction sheet and emergency contact information.
- At least one high sensitivity pregnancy test.

The patient should take misoprostol 800 mcg sublingually or vaginally every 3 hours for at least 3-4 doses. The patient may choose either route for each dose. If using vaginal administration, moistening each tablet with a few drops of water before insertion may improve effectiveness. The patient should take the extra dose if no more than scant bleeding occurs or the patient is not sure that the pregnancy has passed, or if instructed to do so by the clinician.

FOLLOW-UP

Outcome assessment is important after use of a misoprostol-only regimen. The risk of ongoing pregnancy and need for further treatment is higher with misoprostol-only than with regimens that include mifepristone. The follow-up plan may include a self-administered symptom checklist or an in-person or remote contact one week after dispensing treatment. If the patient reports indicators of continuing pregnancy or ectopic pregnancy, evaluate with ultrasound or serum HCG tests.

In addition, plan a test to confirm abortion completeness. The test should be one of the following:

- High sensitivity urine pregnancy test. The patient may perform the test at home 4 weeks after misoprostol use. If the test is positive, evaluate with ultrasound or serum HCG tests. A second urine pregnancy test a week after the first may be recommended if patient history otherwise suggests likely complete abortion.
- Ultrasound or pelvic examination. This test may be done 1-2 weeks after misoprostol ingestion or as soon as the patient believes the pregnancy has been expelled; however, longer intervals may decrease the chance of documenting an incomplete abortion that will later resolve.
- Serial serum HCG testing. Perform the first test on the day of initial misoprostol ingestion, and the second 1-2 weeks later. Interpret the decline according to standards for abortion with mifepristone and misoprostol.

MANAGEMENT OF TREATMENT FAILURES

Treat ongoing pregnancy with uterine evacuation or a standard regimen of mifepristone and misoprostol if available. If these treatments are not immediately available, or if ongoing pregnancy is excluded by ultrasound or the viability of the pregnancy is unknown, additional doses of misoprostol may be prescribed. Discuss the risk of birth defects due to misoprostol exposure if the patient wishes to continue the pregnancy or may face barriers to additional treatment.

Fig. 1. Sample protocol for provision of medication abortion with misoprostol-only.

the patient has had no more than scant bleeding within 3 hours after the last dose or is not sure that the pregnancy has passed, the patient should take the extra dose.

The protocol recommends that the patient should self-administer the doses sublingually or vaginally, according to patient preference at the time of each dose. Patients should not simply swallow the pills. Although

TAKING THE MISOPROSTOL

1. Each dose of misoprostol is 4 pills.* You may choose to take the pills either of two ways:
   - Sublingually: Put a dose of 4 pills under your tongue. Leave them there for 30 minutes, and then swallow what's left of the pills with water.
   - Vaginally: Wash your hands, then lie down and use your finger to insert a dose of 4 pills as high up into your vagina as you can reach. Moistening the tablets with a few drops of water before you insert them may help them work better. Stay lying down for 30 minutes. Don't worry if pieces of the tablets come out after that point, as the medicine has already been absorbed. Pieces of the tablets may remain in the vagina for days.
2. Take one dose of 4 pills every 3 hours until you have taken 3 or 4 doses in all, as recommended by your provider. Take the doses either sublingually or vaginally. You can use either route for each dose. Continue to take the medication as directed even if you are bleeding or having pain or other symptoms.
3. Take an additional dose of 4 pills sublingually or vaginally if you have had only light or no bleeding within 3 hours after the last dose or if you do not feel you have passed the pregnancy.

MANAGING SYMPTOMS

You may begin to bleed within 1 to 4 hours after the first dose of misoprostol. Bleeding can last 2 weeks or sometimes longer. Use ibuprofen and acetaminophen for pain, cramping, and fever. The first dose of these medications may be taken 30 minutes before misoprostol and continued as needed. For nausea, vomiting, and diarrhea, use prescription medications prescribed by your abortion provider or use over-the-counter medications such as dimenhydrinate and loperamide.

CONTACT YOUR PROVIDER IF:

- You are unable to take all of the misoprostol doses recommended by your provider.
- One week after taking misoprostol, you have any of the following symptoms of possible continuing pregnancy:
  - You have had only light or no bleeding.
  - You do not feel that you passed the pregnancy.
  - Your pregnancy symptoms (such as nausea and breast tenderness) are not resolving.
- Any time you have any of the following:
  - Fever of 100.4°F or higher more than 24 hours after the last dose of misoprostol.
  - Severe or increasing pain or cramps that don't get better with pain medicine, rest, or heating pads.
  - Bleeding that soaks through 2 maxi pads an hour for 2 hours or more.
  - Symptoms of allergic reaction (rash, shortness of breath).
  - Any concerns or questions.

CONFIRMING THAT THE ABORTION IS COMPLETE

You should have a test to make sure that the misoprostol worked. Your provider will recommend one of the following:

→ Ultrasound or pelvic exam
→ Blood tests on the day you take the misoprostol and 1-2 weeks later
→ Urine pregnancy test 4 weeks after you take the misoprostol. You may do this yourself at home. If the result is positive or unclear, contact your provider. Do not do this test earlier than 4 weeks because if you do, you are likely to get a positive result even if the medications worked and you are no longer pregnant.

If you are unable to do the recommended test on time, contact your provider to arrange an alternative test.

**This instruction sheet assumes that each pill contains misoprostol 200 mcg. If not, adjust as needed.*

Fig. 2. Sample instructions for patients receiving medication abortion with misoprostol-only.

sublingual administration may cause more side effects, it also may be more practical, especially if the patient is bleeding. Vaginal administration may be more comfortable than sublingual dosing if the patient is nauseated. If the patient chooses that route, moistening the tablets with a few drops of water before administration may enhance effectiveness. Moistening may be logistically difficult for patients, however. Patients should be informed that remnants of the tablets may be visible in the vagina days after insertion.

The protocol recommends providing the patient with at least one urine pregnancy test, even if a different follow-up test is planned, in

order to enable self-assessment if the patient does not obtain the planned test.

3.4. Symptom management

Misoprostol causes uterine cramping, nausea, and vomiting, and some research studies report a higher incidence of fever, chills, and diarrhea [4,6,39,40] after misoprostol-only regimens than after mifepristone and misoprostol. Thus, the sample protocol specifies that clinicians should provide or recommend antipyretics, analgesics, antiemetics, and antidiarrheal medication. Studies of patients treated with mifepristone and misoprostol have indicated that for pain relief, ibuprofen was superior to acetaminophen [46] and that transcutaneous electrical nerve stimulation [47] and prophylactic use of ibuprofen combined with metoclopramide [48] may be useful. One comparative study found that loperamide reduced diarrhea [49].

3.5. Follow-up

Limited data are available on the expected timing or duration of patient symptoms after successful abortion with misoprostol-only. The expected rate of decline of HCG levels in urine or serum is also unknown. The sample protocol assumes that both symptoms and laboratory markers of successful abortion will occur similarly after use of misoprostol with or without mifepristone. The recommended follow-up approach in the sample protocol is therefore consistent with commonly used clinical approaches used after treatment with mifepristone and misoprostol.

Specifically, each patient should have a follow-up plan, which may include a self-administered symptom checklist with instructions on when to contact the provider or a scheduled in-person or telemedicine encounter 1 week after treatment to assess symptoms. Abortion completeness should be confirmed with a test: either a high-sensitivity urine pregnancy test performed at home 4–5 weeks after treatment or an ultrasound, pelvic examination, or serum serial HCG tests. The results of these evaluations should be interpreted and managed according to standards for the assessment of patients using mifepristone and misoprostol.

However, clinicians should be aware that if HCG levels decline more slowly after treatment with misoprostol-only, then documenting complete abortion using urine pregnancy tests or serial serum HCGs may take longer than would be expected after abortion with mifepristone and misoprostol. Although a slow decline is not likely to increase the risk of missing a treatment failure or ectopic pregnancy, it may mean that patients using misoprostol-only may require more post-treatment contacts and evaluations to confirm treatment success than is typical after the use of regimens containing mifepristone. Nevertheless, because of the higher risk of ongoing pregnancy after treatment with misoprostol-only, all post-treatment symptoms or signs that the pregnancy may be continuing, including a positive urine pregnancy test 4 weeks after treatment, should be further evaluated.

3.6. Management of treatment failures

Ongoing pregnancy or incomplete abortion after the use of misoprostol-only may be managed with a uterine evacuation procedure, a standard regimen of mifepristone and misoprostol if available, or additional misoprostol doses. No data are available that establish the effectiveness of continued misoprostol dosing to terminate a viable pregnancy that has already been exposed to three or more prior doses. Thus, if ongoing pregnancy has been definitively diagnosed, the first two of these alternatives are preferred, although additional misoprostol also may be useful if the patient will not be able to immediately obtain other treatments. If the pregnancy is no longer viable or if the viability of the pregnancy is unknown, and the patient does not have heavy bleeding or other acute symptoms mandating immediate treatment, additional misoprostol is a reasonable primary option. Data indicate that treatment success may increase with the amount of time between treatment and the decision to intervene [21], suggesting that when clinically appropriate, conservative management can be beneficial.

4. Patient education

Patients should be reassured that misoprostol-only is a well-studied and recommended regimen for abortion.

Every patient contemplating medication abortion with misoprostol-only should receive sufficient education to understand the risks, benefits, and alternatives to the regimen, including uterine evacuation and treatment with mifepristone and misoprostol if available, to enable an informed choice. Counseling should be tailored to each patient's individual situation. Patients using misoprostol-only may experience more immediate, intense, and prolonged side effects than those using a mifepristone regimen. The risk of treatment failure requiring additional medications or a procedure (about 10%) is higher after misoprostol-only than after regimens containing mifepristone. About 3% to 6% of patients using misoprostol-only may have an ongoing pregnancy. Patients should be informed that misoprostol can be teratogenic if the pregnancy is not terminated; prospective studies have suggested that exposure in early pregnancy may double the risk of cranial nerve anomalies, limb defects, and other major birth defects [50,51]. However, for patients who cannot readily obtain or prefer not to use mifepristone, a misoprostol-only regimen is a reasonable option.

To minimize risk and identify treatment failures promptly, patients should take all doses of misoprostol recommended by the abortion provider. The patient should be attentive to signs of possible treatment failure or complications and should have or perform the planned follow-up test. If the patient is unable to complete the prescribed regimen or to obtain or perform the follow-up test, the patient should contact the provider.

A sample instruction sheet for patients is provided in Figure 2.

5. Conclusion

After more than 22 years on the U.S. market and clinical use for more than 3 decades throughout the world, the safety and effectiveness of mifepristone are conclusively established. From a medical perspective, to prohibit the use of this drug for abortion care is senseless. However, even if legally available, mifepristone may not be accessible to some patients due to cost, telehealth regulations, distribution restrictions, contraindications, or personal reasons. Offering medication abortion with misoprostol-only is a safe, effective, patient-centered approach to enable continued access to this essential health service.

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