

NAF PROTOCOL FOR MIFEPRISTONE/MISOPROSTOL IN EARLY ABORTION IN THE U.S.

Note: This NAF protocol describes the U.S. FDA-approved labeling for mifepristone as well as evidence-based alternatives to that regimen.¹

BACKGROUND INFORMATION

1. Mechanisms of action of mifepristone and misoprostol
2. Pharmacokinetics
3. Efficacy, benefits
4. Side effects
5. Acceptability

ELIGIBILITY:

1. Women considering medical abortion with mifepristone and misoprostol:
 - a. Should not have any of the following:
 - hemorrhagic disorder or concurrent anticoagulant therapy;
 - chronic adrenal failure;
 - concurrent long-term system corticosteroid therapy;
 - confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass;
 - inherited porphyrias;
 - IUD in place (must remove before treatment);
 - history of allergy to mifepristone, misoprostol or other prostaglandin; and
 - unwillingness to undergo a vacuum aspiration (if medically indicated).
 - b. Should have gestation no more than 49–63 days depending on the regimen used;² confirmation by ultrasound may be used routinely and is essential if there is a question whether the duration of the pregnancy is within the guidelines or if an ectopic pregnancy is suspected.
 - c. Must be able to give informed consent and comply with treatment requirements, receive the Mifeprex™ Medication Guide, and sign the Mifeprex™ Patient Agreement and any additional consent forms.
 - d. Should have access to a telephone and transportation to a medical facility equipped to provide emergency treatment for serious complications, including prompt evacuation of the uterus and blood transfusion for hemorrhage.
2. Special considerations:
 - a. There are limited data available on the effects of mifepristone or misoprostol while breastfeeding. An international consensus meeting held in 2004 suggested that until

¹ Note: Certain state and local regulations may specifically affect abortion practice, including the use of medications in abortion care. It is sound management for providers to be aware of such regulations.

² See Evidence-Based Alternative Regimens below. Gestation is commonly referred to in terms of days since the last menstrual period (LMP). Since clinicians establish gestational age based on history, physical exam, and/or ultrasound, gestational age as estimated by the clinician may not always be consistent with the historical LMP.

further evidence is made available, clinicians may choose to advise patients to refrain from breastfeeding (i.e. pump and discard breast milk) for at least 2 days after taking mifepristone and at least 6 hours after misoprostol.

- b. As in the case of surgical abortion, current severe anemia should be considered when assessing eligibility. Most research studies of medical abortion regimens have not included women with a hemoglobin <10 gm/dl.
- c. Any patient with serious systemic illness (e.g., severe liver disease, significant cardiac disease, renal failure, uncontrolled seizure disorder) should be evaluated individually to determine the safest method of pregnancy termination.

COUNSELING, EDUCATION and INFORMED CONSENT should be conducted in compliance with applicable state and local laws, ordinances, regulations, and common law governing the consent process and standard of care for abortion provision, and should include:

1. Discussion of the decision to have an abortion and assurance that the decision is the patient's own (i.e. without coercion).
2. Discussion of abortion methods (e.g. medical abortion, vacuum aspiration) and the risks and benefits of each in relation to the alternative of continuing the pregnancy, including the risk of death for all options.
3. Discussion of known side effects and possible complications of abortion with mifepristone and misoprostol. This should include:
 - a. information about expected side effects and the differences between side effects and complications; for example, which symptoms warrant contacting the provider immediately:
 - i. soaking 2 or more maxipads per hour for 2 consecutive hours;
 - ii. sustained fever >38°C (100.4°F) or onset of fever more than 24 hrs after taking misoprostol;
 - iii. abdominal pain or discomfort, or "feeling sick" including weakness, nausea, vomiting or diarrhea *more than 24 hours after taking misoprostol*;
 - iv. light bleeding or spotting, accompanied by one-sided, severe lower abdominal pain, with dizziness, shoulder pain or shortness of breath, particularly when an IUP was not confirmed by pre-treatment ultrasound (these symptoms are strongly suggestive of rupturing ectopic pregnancy and the clinician should assist with arranging the patient's immediate access to emergency services).
 - b. An explanation that although medical abortion does not cause ectopic pregnancy, and that neither the medications nor the route of their administration have been determined to cause infection, it is important to have access to a provider who is familiar with the signs and symptoms of these rare but serious complications of pregnancy and abortion.
 - c. An explanation of the importance of a follow-up visit to confirm complete abortion, including information about the likelihood of continued pregnancy in the absence of bleeding, the possibility of continued pregnancy even after bleeding, and that fetal malformations have been reported after first trimester use of misoprostol. Therefore,

women must be strongly advised to complete the abortion, either medically or with vacuum aspiration, once these medications have been taken.

4. Anticipatory guidance for the length of time involved in the medical abortion process and the need for multiple visits. The FDA-approved regimen (mifepristone 600mg followed by misoprostol 400µg orally up to 49 days' gestation) calls for at least 3 visits; however, alternative evidence-based regimens usually require only two. In the FDA-approved regimen, approximately two-thirds of all women will abort within 4 hours of taking misoprostol, and about 90% of women will abort with 24 hours. However, complete expulsions may be more rapid in evidence-based regimens using 800µg of either vaginal or buccal misoprostol.
5. Instruction concerning the administration of misoprostol: for the buccal regimen, this includes the importance of retaining the tablets between cheek and gum for 30 minutes prior to swallowing the residual; for vaginal regimens, hand washing prior to placement deep in the vagina.
6. Anticipatory guidance for the variation in pain experienced by women and the use of pain medications. Pain is typically described by women as cramping and is self-limiting; it is often most intense during the actual expulsion of the pregnancy, commonly for a 2-4 hour period, although possibly preceded and followed by intermittent mild cramping. Once treatment has been initiated, the patient should have ready access to a supply of pain medication and instructions for use.
7. Anticipatory guidance for the amount and quality of bleeding and the passage of tissue associated with the abortion process, including the following key points:
 - a. bleeding is typically heavier than menses; this may be influenced by the duration of the pregnancy;
 - b. the passage of clots is common; women should be reassured that at this stage of pregnancy clots do not represent a placenta;
 - c. in the earliest pregnancies an embryo is usually not distinguishable, but even when the gestation is close to 9 weeks and the embryo may be visible, it is very small and often passes unnoticed within a clot;
 - d. although women may start spotting or bleeding in the interval between using mifepristone and misoprostol, misoprostol should still be used as instructed;
 - e. when women use maxi-pads, the assessment of bleeding can be applied to a common standard of measurement for determining whether the amount of bleeding is within the normal range;
 - f. patients should be instructed to contact their provider if there has been little or no bleeding within 24 hours following administration of misoprostol (note: in the absence of any other signs of symptoms of complications, this is not an emergency);
 - g. women should be advised that they may (rarely) experience a second episode of heavy bleeding several weeks to months after initiating medical abortion; this event is distinct from the more commonly experienced heavy first menses which may occur after either a medical or surgical abortion.
8. A review of the manufacturer's Medication Guide (which should be given to the patient along with a copy of the signed Patient Agreement), as well as an individualized consent to abortion. *If*

the provider is using an evidence-based regimen that differs from the FDA-approved regimen, the individualized informed consent should detail the evidence-based regimen being used and should specify how the regimen differs from the FDA-approved labeling.

9. Information regarding privacy and confidentiality precautions.
10. A review of aftercare instructions, including 24-hour emergency contact information.
11. The availability of contraception and contraceptive counseling, with initiation of contraception, if desired by the patient, as soon as possible. Clinicians' individual practices in the timing of initiation of contraceptive methods following medical abortion vary, but self-administered hormonal methods such as oral contraceptives may be safely initiated at any time. Because women may both regain fertility and resume sexual intercourse prior to their follow-up visit (regardless of instructions to the contrary) it is helpful to offer options, supplies and instructions at the first visit.

MEDICAL HISTORY and PHYSICAL EXAMINATION should include:

1. pertinent medical and obstetrical history, including history of allergies and all current medications;
2. vital signs and pertinent physical examination as indicated; and
3. determination of gestational age by clinical assessment (ultrasound may be used in place of, or in addition to bimanual pelvic examination).

LABORATORY EVALUATION should include:

1. test to confirm pregnancy; a qualitative (urine) hCG* is routine;
2. documentation of Rh status;
3. hemoglobin or hematocrit (recommended); and
4. other tests as medically indicated.

**Serial quantitative β -hCG levels are not required except as part of an evaluation for ectopic pregnancy, molar pregnancy, or certain complications, such as post-treatment retained products of conception.*

ULTRASOUND EXAMINATION:

1. Although medical abortion researchers and many providers in the U.S. routinely utilize sonography to confirm gestational age and abortion outcome, in other countries with long experience in safe medical abortion practice sonography is reserved for special situations (discrepant size and dates, inability to palpate the uterus, risk of ectopic pregnancy, etc.).
2. In relation to the use of ultrasound, the following points should be considered:
 - a. When a bimanual uterine examination is not routinely performed by experienced providers, and whenever clinical findings are inconclusive or worrisome, either transabdominal or transvaginal ultrasound should be used to confirm intrauterine gestation and the estimated gestational age.

- b. If pregnancy is not definitively identified by transabdominal ultrasound, the more sensitive transvaginal approach should be used.
 - c. Whenever ultrasound examination is performed prior to medical abortion, examiners should be able to demonstrate competence in limited sonography for first-trimester pregnancy. Relevant findings (yolk sac, gestational sac, embryonic pole, presence of cardiac activity, etc) should always be documented for the medical record.
3. If an embryonic pole is visible, the crown-rump length (CRL) measurement should be used for calculating gestational age.
4. If only the gestational sac is visible, the measurements of diameter should be taken in three planes to calculate the MSD (mean sac diameter), which is the appropriate unit for estimating gestational age prior to the appearance of the fetal pole.
5. If an intrauterine gestational sac is not identified, the differential diagnosis includes early intrauterine pregnancy, ectopic pregnancy, and abnormal intrauterine pregnancy. Further evaluation, referral or treatment may be warranted.

For example, the following situations are highly suspicious for ectopic pregnancy:

- abdominal pain with an adnexal mass on physical exam;
- a quantitative serum β -hCG of greater than 2000 mIU/ml with no intrauterine sac seen using transvaginal ultrasound, or greater than 3600 mIU/ml with no intrauterine sac seen using abdominal ultrasound.

These findings necessitate urgent attention, patient education and guidance, and further evaluation (including diagnostic imaging, which is beyond the scope of most individual ob/gyn or primary care practices). Although in many cases methotrexate may be used to treat early ectopic pregnancy, emergent surgical intervention to prevent or manage rupture may still become necessary.

In short, if a combination of history, physical and sonographic findings suggest a possibility of ectopic pregnancy, the provider must follow standards of gynecological care which are beyond the scope of this document (see the references to this document and the NAF *Clinical Policy Guidelines*, “Early Medical Abortion” for further discussion and resources). Mifepristone should not be administered until a suspected ectopic pregnancy has been definitively ruled out.

MEDICATION and FOLLOW-UP:

I. FDA-APPROVED LABEL

Clinicians should be familiar with the manufacturers' labeling and offer patients the corresponding educational materials; this information is beyond the scope of this document but is available from Danco Laboratories.*

Medications must be administered by or under the supervision of a physician able to: assess the pregnancy's gestational age; diagnose ectopic pregnancies; provide vacuum aspiration intervention or have plans in place to provide such care through others if needed; and assure patient access to emergency medical facilities equipped to provide blood transfusions and emergency resuscitation during the treatment procedure.

A brief outline of the regimen follows:

DAY 1:

- a. Mifepristone 600 mg (three 200 mg tablets) is given as a single oral dose.
- b. Rh immune globulin is administered to Rh-negative patients.

DAY 2:

The patient returns to the provider. Unless abortion has occurred, 400 µg (two 200 µg tablets) of misoprostol are given as a single oral dose.

DAY 14:

The patient returns for a follow-up visit on approximately day 14 to be assessed for completion of abortion. Vacuum aspiration is recommended if a viable pregnancy is detected at this time by ultrasonography, because of the risk of fetal malformation if the pregnancy were to continue.

*Danco Laboratories
www.earlyoptionpill.com
1 (877) 432-7596

II. EVIDENCE-BASED ALTERNATIVE REGIMENS

Individual providers are not limited to the indications or regimens set forth in FDA-approved labeling (although in order to acquire the medication from the U.S. distributor they are subject to the terms of the U.S. manufacturer's *Prescriber's Agreement*). FDA policies explicitly permit the evidence-based use of approved medications. The expectation of the FDA is that providers will be guided by accepted medical standards and guidelines when determining whether to use drugs in alternative evidence-based regimens rather than as labeled.

KEY FINDINGS FROM ALTERNATIVE REGIMENS RESEARCH

1. Mifepristone 200 mg is as effective as mifepristone 600 mg in all published studies.
2. Home administration of misoprostol has been found to be safe and effective and is highly acceptable to patients.
3. Compared to regimens using misoprostol 400 µg orally, regimens using misoprostol 800 µg vaginally increase the proportion of women with onset of bleeding and likely expulsion of pregnancy within 4 hours of misoprostol administration.
4. In regimens using 200 mg mifepristone and 800 µg misoprostol administered vaginally, studies show equivalent efficacy when misoprostol is administered in the interval between 6 and 48 hours after mifepristone. One study suggests that up to a 4% loss of efficacy may be observed when misoprostol is administered simultaneously with mifepristone, but that safety and acceptability are otherwise comparable. In all cases, a success rate of $\geq 95\%$ has been shown to persist through 63 days gestation.
5. In regimens using 200 mg mifepristone and 800 µg misoprostol administered buccally, efficacy is comparable to vaginal administration. To use the buccal route, women place 2 tablets of misoprostol 200 µg in each cheek (total of 4 tablets) for 30 minutes, one to two days after mifepristone (any remnants of tablets are to be swallowed after 30 minutes).
6. One large retrospective study suggests that a change of route from vaginal to buccal administration of misoprostol after mifepristone was associated with a reduced incidence of serious infection, although absolute risk is exceedingly low.
7. The sublingual route of misoprostol administration has been associated with a rapid onset of action and high systemic bioavailability, but also a high rate of unpleasant side effects when given for abortion in doses of 800 and 600 µg. However, in regimens using 200 mg mifepristone and 400 µg misoprostol administered sublingually 24 hours after mifepristone, efficacy does not decline significantly with advancing gestational age up to 63 days, and rates of reported side effects appear comparable to those associated with regimens using 800 µg vaginal misoprostol.
8. Compared to regimens using vaginal and buccal misoprostol, a single 400 µg dose of oral misoprostol following mifepristone has been reported to be less effective at gestations beyond 49 days. A somewhat higher efficacy of oral misoprostol at later gestations (up to 63 days) may be achieved by an initial dose of 800 µg (which may be given in 2 divided doses of 400 µg each, 2 hours apart). However, the oral route of administration is strongly associated with higher failure

rates as the duration of gestation increases, and up to 10% of women beyond 49 days gestation have been reported to need an additional dose of 800 µg misoprostol, administered vaginally, when evaluated on Day 7 following mifepristone.

9. The initial follow-up evaluation can occur as soon as the woman feels confident that she has passed her pregnancy. In studies with earlier follow-up, ultrasound or serial β -hCG levels have been used to confirm completion. No studies have evaluated the safety, efficacy or acceptability of any regimen with an interval to first follow-up longer than (approximately) 14 days.
10. When incomplete abortion or continuing pregnancy is diagnosed at the follow-up visit, the clinician and the patient have several management options, including expectant management (waiting), the administration of additional misoprostol, and aspiration completion. Which option is chosen depends on the diagnosis, the time elapsed since mifepristone, the actual gestational age at the time of follow-up, patient preference and clinical judgment.
 - Aspiration completion is the standard treatment for a continuing pregnancy at 14 days following mifepristone.
 - At first follow-up for abortion within 11 days of treatment using mifepristone and vaginal misoprostol, more than ½ of women with incomplete abortion/interrupted pregnancy (either a persistent fetal pole without cardiac activity, or a persistent gestational sac on ultrasound) were reported to successfully expel the pregnancy when treated with a second dose of 800 µg vaginal misoprostol. In cases of continuing pregnancy (as demonstrated by persistent cardiac activity on ultrasound within 11 days of treatment) approximately 1/3 of women were reported to successfully abort after a second vaginal dose of misoprostol. This data includes pregnancies up to 74 days LMP by the time of their follow-up visit.
 - The World Health Organization lists misoprostol as an “essential medicine” for the treatment of incomplete abortion.
11. Absent a persistent gestational sac or fetal pole, the diagnosis of incomplete abortion and indications for aspiration completion should be based on a combination of history, physical exam, and ultrasound findings, rather than on ultrasound imaging alone. Studies have not demonstrated a useful management correlation between indistinct sonographic findings and either pathology or clinical outcome.
12. All women given a supplemental dose of misoprostol for continuing pregnancy or incomplete abortion should be prepared to return for an evaluation visit (1-8 days later) to ensure complete abortion.

COMPARISON OF FDA-APPROVED AND OTHER EVIDENCE-BASED REGIMENS FOR MIFEPRISTONE AND MISOPROSTOL IN EARLY ABORTION

	FDA LABELING	ALTERNATIVE: LOW-DOSE MIFEPRISTONE AND ORAL MISOPROSTOL BEYOND 49 DAYS	ALTERNATIVE: LOW-DOSE MIFEPRISTONE AND VAGINAL MISOPROSTOL	ALTERNATIVE: LOW-DOSE MIFEPRISTONE AND BUCCAL MISOPROSTOL	ALTERNATIVE: LOW-DOSE MIFEPRISTONE AND SUBLINGUAL MISOPROSTOL
MIFEPRISTONE DOSE	600 mg p.o. (3 tabs)	200 mg p.o.(1 tab)	200 mg p.o.(1 tab)	200 mg p.o.(1 tab)	200 mg p.o.(1 tab)
MISOPROSTOL DOSE	400 µg p.o. (2 tabs)	800 µg p.o.(4 tabs - may be taken in 2 divided doses, 2 hrs apart)	800 µg p.v.(4 tabs)	800 µg between cheek and gum (4 tabs)	400 µg s.l. (2 tabs)
INTERVAL BETWEEN MIFE AND MISO ADMINISTRATION	48 hrs	1 day.	Simultaneously; at 24 hrs; or between 6-48 hrs <i>N.B. Simultaneous use may be up to 4% less effective than regimens observing an interval of 6-48 hrs</i>	Between 1-2 days at ≤ 56 days EGA; between 24-36 hrs at ≤63 days EGA	24 hrs
LOCATION OF MISO ADMINISTRATION	In the office or clinic	Home	Home	Home	Home
GESTATIONAL AGE RANGE <i>(recommended)</i>	≤49 days	≤56 days <i>N.B. This route is significantly less effective after 56 days.</i>	≤63 days	≤63 days	≤63 days
TIME OF FOLLOW-UP	Day 14 (approximately)	Day 7 (approximately) <i>N.B. When using this regimen up to 63 d. LMP, continuing pregnancy rates approached 10% at followup. Researchers using this regimen repeated misoprostol vaginally when incomplete abortion or continuing pregnancy was noted at 7 days post-mifepristone.</i>	Day 4-14 (approximately)	Day 4-14 (approximately)	Day 4-14 (approximately)

CONCLUSION OF TREATMENT

Comprehensive follow-up care is important. Delivery of all abortion services requires 24- hour availability of a clinician for assessment of potential complications. This is especially critical with medical abortion as the patient is expected to participate in monitoring her own process, and may need assistance in determining whether or not intervention is indicated.

Vacuum aspiration, administration of uterotonic agents, and rarely, intravenous fluid administration or blood transfusion may be necessary for treatment of incomplete abortion with excessive bleeding. Those providers who do not perform vacuum aspiration completion should secure a formal arrangement for back-up.

Vacuum aspiration may also be offered as an option for any patient experiencing unexpected distress with the process of medical abortion (for example, a delay in passage of the pregnancy or excessively unpleasant side effects), if she would prefer vacuum aspiration to expectant management.

Once completion of the medical abortion is confirmed, information on the expected length and quantity of normal post-abortion bleeding, the signs and symptoms of complications, and any pertinent instructions should be provided to the patient. At this time, providers should also follow up with the contraceptive counseling initiated during the first visit, revising method planning and supplies as needed.

SELECTED STUDIES OF REGIMENS USING MIFEPRISTONE/MISOPROSTOL

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These education materials are intended as guidelines and do not dictate an exclusive course of management. These materials contain recognized methods and techniques of medical care that represent currently appropriate clinical practice. Variations in the needs of individual patients and differences in the resources available to clinical providers may justify alternative approaches to those contained in these materials. Neither the National Abortion Federation, its officers, employees, or members are responsible for adverse clinical outcomes that might occur in the course of delivery of abortion services in which they are not expressly and directly involved in the role of primary caregiver.

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