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FAMILY PLANNING (A BURKE, SECTION EDITOR)

Medical Abortion: Use of Mifepristone and Misoprostol in First and Second Trimesters of Pregnancy

Eva Patil · Alison Edelman

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Abstract Medical abortion in the first and second trimesters of pregnancy offers women a safe and effective alternative to surgical termination. The World Health Organization supports a combination of mifepristone and misoprostol as the optimal regimen in both the first and second trimesters of pregnancy, but doses, routes, and timing of administration vary with gestational age. Most methods of contraception can be initiated at the time of medical abortion in women wishing to delay fertility, with the exception of the intrauterine device, which can be initiated as soon as a woman is no longer pregnant.

Keywords Medical abortion · Mifepristone · Misoprostol · Medical induction of labor termination

Introduction

The most recent abortion surveillance data from the Centers for Disease Control (CDC) in 2010 reported 765,651 abortions in the US, at a ratio of 228 to every 1,000 live births. Of these, medication-induced abortions accounted for 26.5 % of abortions less than or equal to eight weeks gestation and 0.7–3.8 % of abortions at higher gestational ages [1]. Although medical abortions (MAs) do not account for the majority of abortions in the U.S., this option is extremely safe with serious complication rates of<1 %, and it offers women options, especially when living in areas without health care providers trained in vacuum aspiration [2••]. The World Health Organization (WHO) supports a combination of mifepristone and misoprostol as the recommended regimen for both the first and second trimesters of pregnancy, but doses, routes, and timing of administration vary with gestational age [3]. This article will review the indications, regimens, side effects, and potential complications of these two medications in both first and second trimester MAs.

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E. Patil (✉) · A. Edelman
Oregon Health & Science University, Mail code UHN 50, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, USA
e-mail: patile@ohsu.edu

A. Edelman
e-mail: edelmana@ohsu.edu

Pharmacology

Misoprostol

Misoprostol, also known as Cytotec, is a synthetic analogue of prostaglandin E1. Although only approved by the US Food and Drug Administration (FDA) in 1988 for the prevention of stomach ulcers, misoprostol has many off-label uses applicable to obstetrics and gynecology [4]. Misoprostol is used for cervical ripening in labor induction, management of postpartum hemorrhage, cervical preparation for transcervical procedures, miscarriage management, as well as first and second trimester pregnancy termination [5]. Misoprostol is the preferred commercially-available prostaglandin, because it is affordable, widely available, remains stable at room temperature in non-tropical climates, and has no known effects on pulmonary bronchi or blood vessels [6].

Misoprostol can be administered via multiple different routes, including orally, sublingually, buccally, vaginally, and rectally. Each route of administration results in a different length of time at which the peak drug level is reached and different overall bioavailability [7–11]. These differences are summarized in Table 1. Although generally well-tolerated by any route of administration, misoprostol given orally or sublingually tends to result in more side effects, such as nausea, vomiting, and diarrhea [13]. Other side effects reported

Table 1 Summary of misoprostol peak concentration, time to achieve peak concentration, and bioavailability based on route of administration [7, 9, 12]

Route of administration	Time to peak concentration	Peak concentration (mean pg/ml±SD)	Area under the Curve (AUC_{T1}±SD/AUC_{T2}±SD) (pgxh/ml)
Oral	30 min	287.6±144.3	369.3±155.2/402.8±151.6 [a]
Sublingual	30 min	574.8±250.7	702.1±274.8/743.7±291.2 [a]
Buccal	75 min	264.8±170.7	475.2±312.9/519.6±338.8 [b]
Vaginal	70-80 min	125.2±53.8	329.7±139.0/433.7±182.6 [a]
Rectal	40-65 min	202.2±195.7	280.9±275.5/312.5±280.6 [b]

Area Under the Curve (AUC) is a proxy for bioavailability

[a] AUC measured at 240 (T1) and 360 (T2) minutes

[b] AUC measured at 240 (T1) and 300 (T2) minutes

include an unpleasant taste when taken sublingually or buccally, abdominal pain and cramping, headache, and fever and chills when used in high doses [9]. Side effects are dose-dependent, and using the vaginal route of administration can reduce gastrointestinal (GI) effects [14].

Mifepristone

Mifepristone has been FDA-approved for abortion care in the United States since September 2000. It is a derivative of norethindrone and acts directly at the progesterone receptor as a competitive inhibitor. Mifepristone disrupts the progesterone support required during early pregnancy and has multiple effects on the reproductive tract, including increasing uterine contractility, increasing sensitivity to prostaglandin, altering the endometrium causing decidual necrosis, and ripening of the cervix [6, 15–17]. The medication is administered orally, is easily absorbed, undergoes first-pass metabolism in the liver, and reaches a dose-independent peak concentration within one to two hours when using doses of 100 mg or greater [17, 18]. Off-label uses, including emergency contraception, ovulation suppression and cervical preparation, have been explored [17]. Side effects are most often associated with prolonged daily use and include fatigue, nausea, vomiting, anorexia, and hypokalemia [17, 19].

Contraindications to MA with Mifepristone and Misoprostol

Contraindications to MA with misoprostol and mifepristone include [20–23]:

- Known ectopic pregnancy
- An in situ intrauterine device (IUD) – removal is necessary prior to MA
- Prior allergic or hypersensitivity reactions to prostaglandins or mifepristone, which are extremely rare
- Chronic adrenal failure
- Inherited porphyria

Caution should be used in women with uncontrolled severe medical conditions. No data have been published regarding outcomes in women who are anticoagulated or who have hemorrhagic disorders, and MA for these patients should be considered based on their individual situation. Misoprostol has also been associated with increased risks of uterine rupture in patients with a prior uterine incision undergoing induction of labor at term, and is thus avoided in this population [14, 24]. While it is important to keep these contraindications in mind, they are rare. Overall, misoprostol and mifepristone are safe independently and in combination.

First Trimester Medical Abortion

Patient Counseling

Women must be informed of the advantages and disadvantages of MA or vacuum aspiration when deciding on a method of pregnancy termination. An MA allows the woman to avoid an invasive procedure and significant exposure to anesthetic medications. Many women feel MA to be the more “natural” option, like a miscarriage, and prefer being in the comfort of their own home for the process [25]. The disadvantages include experiencing heavy bleeding at home, timing that can be somewhat unpredictable, and a slightly lower successful completion rate. Additionally, an MA may also require more visits as many MA protocols require a follow-up visit to confirm success or if a woman desires a post-MA IUD for contraception. Vacuum aspiration has the advantage of completion in a more predictable period of time, a slightly higher success rate (99 %), lighter vaginal bleeding, and no need for routine follow-up. However, there

are always small risks of complications with anesthesia or with the procedure itself [26]. Patients tend to find both methods highly acceptable when given a choice, although satisfaction with MA up to 9 weeks tends to decrease with increasing gestational age [27, 28].

Pretreatment Considerations

Once a patient has decided to undergo MA, only a few pretreatment tests need to be considered. First, pregnancy should be confirmed by history and exam, or if there is any uncertainty, with either a urine or serum human chorionic gonadotropin (hCG) test. Blood typing for Rh status is the standard of care in the U.S. and Rh-negative patients should be administered RhD immunoglobulin at the mifepristone-administration clinic visit. A hematocrit or hemoglobin may be indicated if there is clinical suspicion for severe anemia, and some protocols require this testing prior to MA, although there is no evidence to support universal screening. When able, screening should be offered for sexually transmitted infections and treatment offered accordingly [14].

Ultrasound can also be a helpful pretreatment tool in assessing gestational age and confirming intrauterine location and viability. However, clinical assessment of uterine size and lack of symptoms consistent with ectopic pregnancy can provide enough information to proceed with MA. The lack of ultrasound should not prevent an otherwise good MA candidate from receiving care [3, 29, 30].

The need for prophylactic antibiotics in MA is debatable. Rates of infection are low (<1 %) after MA, the majority of which are reported as endometritis or "genital tract infections" and resolve with appropriate treatment. Serious infections requiring hospitalizations are rare (<0.01 %) [31], but concern arose in 2005 when cases of sepsis and death resulting from *Clostridium sordelii* infection after MA were identified in the US and Canada [32]. In response, the Planned Parenthood Federation of America (PPFA) switched from vaginal to buccal administration of misoprostol and later added the routine provision of antibiotics. In a retrospective analysis from 2005 to mid-2008, they found a total reduction of 93 % in serious infections (from 0.93/1000 abortions to 0.25/1000 abortions after change in route of misoprostol administrations, further decreased to 0.06/1000 abortions after adding routine antibiotics) [33]. In a subsequent analysis by PPFA of 233,805 MAs in 2009–2010, rates of infection were found to be 0.016 % [2••]. Although it is difficult to clearly separate the effects of adding an antibiotic regimen from the switch in route of misoprostol administration on the reduction in infections, many providers think the implications of a serious infection outweigh the small risks of a course of antibiotics. However, the Society of Family Planning (SFP), the American Congress of Obstetricians and Gynecologists (ACOG), and the WHO do not currently endorse routine prophylactic antibiotics given the low absolute risk of infection [3, 34].

FDA-Approved Versus Evidence-Based Regimens

The FDA-approved regimen for MA is for gestational ages at 49 days or less. It consists of 600 mg oral mifepristone at the initial clinic visit, followed by another visit 48 hours later, during which 400 mcg of oral misoprostol is administered. This regimen was shown to have a success rate of 92 % at a 2-week follow-up visit [35]. Since FDA approval, alternative regimens have been extensively studied using lower doses of mifepristone, higher doses of misoprostol, home administration of misoprostol, and non-oral misoprostol dosing. These changes have been shown to improve effectiveness at higher gestational ages (63 days), be more convenient for the patient, and have fewer side effects [36–40]. The most commonly used evidence-based regimen involves administration of 200 mg oral mifepristone, followed 24-48 hours later by patient self-administration at home of 800 mcg of vaginal, sublingual, or buccal misoprostol.

While most providers still limit outpatient first trimester MA to less than nine weeks gestation, there is increasing evidence that outpatient MA can be performed safely up to 70 days gestation with similar efficacy, safety, and patient satisfaction [41•, 42••]. More often, late first-trimester MA up to 13 weeks gestation occurs in an inpatient setting with repeated doses of misoprostol until passage of the pregnancy tissue. Failure rates increase with gestational age, as do the number of doses of misoprostol required, time from induction to abortion, risk of needing a surgical procedure, and risk of needing a blood transfusion [43–46]. Despite these findings, the procedure remains safe with a success rate above 90 %, and patients report it to be a desirable option [41•, 42••, 43–48].

Complications

Complications with MA are rare. A systematic review of MAs using evidence-based regimens at 63 gestational days or less reported rates of abortion failure requiring surgical completion at 4.8 %, ongoing pregnancy at 1.1 %, hospital admission at 0.3 %, and blood transfusion at 0.1 % [49]. Incidences of adverse events in adolescents are not different from adults [50]. The aforementioned PPFA database review of over 200,000 MAs found rates of significant adverse outcomes to be 0.65 %, with ongoing pregnancy as the most common (0.50 %). Additionally, the rate of undiagnosed ectopic pregnancies was found to be 0.7/10,000 MAs [2••]. The risk of death associated with MA appears to be about 1/100,000; however, it is difficult to accurately determine causation with such a rare event [51].

Follow-up

An in-person follow-up visit has been the standard of care for women undergoing MA, although this is currently being challenged. Studies have had women return to clinic 1–2 weeks post-mifepristone administration to confirm pregnancy expulsion, often by ultrasonography. Ultrasound should only be used to assess the presence or absence of a gestational sac, since the thickness of the endometrial stripe does not predict the need for a subsequent surgical procedure [52]. Since ultrasound is not readily available in many areas of the world, history and physical exam alone are often used. Serum hCG levels may provide additional information if needed. Studies demonstrate that an 80 % decline in serum hCG one week after MA has a 0.995 positive predictive value of success [53]. Telephone consultations to assess women's symptoms and low-sensitivity urine pregnancy tests done at home can also aid determination of abortion completion when follow-up is challenging [54]. Although most incomplete MAs are surgically managed, providers may instead consider an additional dose of misoprostol; more than half of women will expel the pregnancy with this treatment option [55]. An ongoing pregnancy after MA, however, should be treated with an aspiration procedure [34].

Second Trimester MA

Abortions in the second trimester (up to 24 weeks gestation) account for a minority of the abortions performed worldwide. However, access to safe services is critical; often the women who need these services are among the most vulnerable populations (including youth, women experiencing disruptive life events such as inability to pay rent or multiple recent moves, minority groups, lack of service availability, the poor, the underinsured, and the less educated) [56, 57]. Second trimester abortions are also critical for women with maternal or fetal issues that are often discovered in the second trimester of pregnancy. In a retrospective cohort of 833 women who received a diagnosis of fetal aneuploidy, 81 % chose termination: 86 % of those with diagnoses of autosomal trisomy and 60 % of those with sex-chromosome aneuploidy [58]. Regardless of the abortion indication, providers should understand pertinent regulations around abortion care so patients can receive appropriate care in an expedient fashion.

Patient Counseling

Women seeking second trimester termination should be counseled about the advantages and disadvantages of surgical versus medical abortion. Choices may be limited depending on the indication for abortion due to systems issues, such as limited availability of trained providers and lack of access to specialized equipment. Second trimester surgical abortion is typically performed by dilation and evacuation (D&E), utilizing a combination of vacuum aspiration and specialized forceps. The procedure is safe, with complications occurring in less than 4 % of cases [59, 60]. Patients may prefer D&E as time of completion is predictable, pain can be minimized with anesthesia, and side effects associated with repeated doses of misoprostol can be avoided.

For pregnancies complicated by certain maternal health conditions, fetal anomalies or genetic disorders desiring autopsy and external genetic examination, or if the family wants to see and hold the fetus as part of the grieving process, medical induction for labor termination may be preferable, although there are surgical techniques that can also offer similar advantages (intact D&E). For MA, patients are typically admitted to an inpatient or day-stay ward. Epidurals or intravenous medications should be available for pain management during the expulsion process. The rates of minor adverse events are slightly higher with MA than with D&E, mostly due to need for surgical removal of retained placenta (~5 %) [61]. Most importantly, major complication rates with second trimester MA are less than 1 % [59, 60, 62].

Pretreatment Evaluation

Pretreatment evaluation prior to MA in the second trimester is the same as in the first trimester. Antibiotic prophylaxis is not necessary for induction termination [3, 63]. Gestational dating by ultrasound is routine in many developed countries. Assessment of uterine size by exam is usually sufficient and ultrasound is not required [3, 29, 30], but should be considered in patients with a history of prior cesarean section or uterine scar, as they are at increased risk of abnormal placentation [64]. History of cesarean section is not a contraindication to second trimester MA or induction termination. The risk of uterine rupture with the use of misoprostol is extremely rare (<0.3 %) [65–69]. If significant concern for abnormal placentation exists, it is preferable for patients to undergo D&E at a tertiary care center where management for severe hemorrhage is immediately available.

Induced Fetal Demise

Some patients may elect to undergo a feticidal injection prior to second trimester MA to avoid transient fetal survival after delivery. The WHO recommends considering feticidal injection for women with gestations over 20 weeks to avoid transient fetal survival [3], whereas the Society of Family Planning (SFP) does not provide a specific recommendation, but suggests a feticidal injection may be considered for the comfort of both the woman and the staff caring for her [70]. Studies are lacking regarding a clear medical benefit to feticidal injection, but there may be compelling social, political, and/or emotional concerns motivating the decision.

The most commonly used agents are potassium chloride (KCl) administered as a fetal intracardiac injection and digoxin administered via intra-amniotic, intrafetal or fetal intracardiac injection. Intracardiac KCl injections require a skilled provider who can accurately deliver the medication to the fetal heart. In a retrospective cohort of 192 women receiving feticidal KCl in an academic perinatology center, fetal asystole was successfully achieved in 99.5 %. Only one complication of maternal seizure was reported, which occurred after needle insertion but prior to injection of KCl [71]. Digoxin is easier to administer as intracardiac injection is not required. A retrospective cohort study of patients undergoing D&E between 18 and 24 weeks included 513 controls and 566 patients who received digoxin, and revealed statistically significant higher rates of spontaneous abortion (zero patients vs. 11), infection (three patients vs. 19), and need for hospital admission (zero patients vs. 11) in the digoxin group compared to controls, but hemorrhage requiring transfusion, uterine perforation and cervical lacerations were uncommon and not significantly different between the two groups [72]. In contrast, other larger retrospective cohort studies have not shown increased risks of infection or extramural delivery in patients receiving feticidal digoxin prior to D&E [73, 74]. Digoxin administered transvaginally instead of transabdominally also has acceptably low rates of ruptured membranes, infections, and extramural deliveries [75]. There are limited data to suggest feticidal KCl injection may decrease time to expulsion and number of doses of misoprostol required [76]. Given the lack of clear data demonstrating medical benefits of feticidal agents, use should be focused on patients for whom avoidance of transient fetal survival is preferred.

Mifepristone and Misoprostol Evidence-Based Regimens

Many studies have examined the ideal dosing, route of administration and timing of mifepristone and misoprostol regimens for MA up to 24 weeks gestation. As in first trimester MA, misoprostol preceded by a dose of mifepristone is the most effective regimen resulting in shorter times to expulsion, and 200 mg of mifepristone is as effective as higher doses [70, 77–81]. The WHO, SFP and ACOG recommend 200 mg of oral mifepristone, followed 24-48 hours later by a loading dose of 800 mcg misoprostol vaginally and an additional 400 mcg misoprostol vaginally every 3 hours until expulsion. If expulsion has not occurred after five doses, the woman may take a 12-hour break before resuming misoprostol dosing [3, 70, 82]. Regimens using sublingual, vaginal or buccal misoprostol administration with or without a vaginal misoprostol loading dose have all been shown to be equally effective [70, 81, 83••, 84–89]. Oral misoprostol dosing is typically avoided, as it leads to more side effects and longer intervals to expulsion [81, 83••, 88]. These evidence-based regimens result in 95 % of patients with gestations less than 24 weeks experiencing expulsion by 24 hours [70].

A recent systematic review examining the impact of a shorter mifepristone-to-misoprostol interval on induction time (first misoprostol dose administration to expulsion) and total time (mifepristone administration to expulsion) revealed that administering the first misoprostol dose 12–24 hours after mifepristone lengthened induction time by 1–2 hours, but shortened total time by at least 18 hours without decreasing safety or efficacy [90•]. Although there are alternate regimens using misoprostol only, other prostaglandins, oxytocin or mechanical cervical dilation, the combination of mifepristone and misoprostol leads to the highest efficacy, shortest induction times, and a high safety profile.

Complications

The majority of complications related to second trimester MA are associated with retained placenta, requiring intervention in approximately 3–5 % of patients when a combined mifepristone and misoprostol regimen is used [61, 70, 79]. However, in contrast to term labor and delivery, there is no set time within which the placenta must be delivered as long as a patient is stable without heavy bleeding [70]. Expectant management and continued dosing of misoprostol will generally result in placental expulsion and avoid the need for further intervention.

Hemorrhage is a rare complication of second trimester MA (0.7 %). It can be caused by atony, retained tissue, abnormal placentation, coagulopathy, or cervical or vaginal laceration. In general, it is managed in the same manner as other obstetric hemorrhages [78, 91•]. The SFP definition of hemorrhage is "both a clinical response to excessive bleeding, such as transfusion or admission, and/or bleeding in excess of 500 mL" [91•]. Per SFP guidelines, management should involve a systematic approach, starting with an exam with or without an ultrasound, followed by repair of a laceration or uterine massage and uterotonics for atony. If these steps fail, resuscitative measures and laboratory studies should be initiated and uterine aspiration or balloon tamponade considered. Lastly, uterine artery embolization and/or surgical exploration with possible need for hysterectomy should be considered [91•]. Special considerations or precautions may be needed for patients with risk factors for hemorrhage. Although hemorrhage can be a traumatic event for both the patient and the care team, it is important to remember this is a rare complication, and induction termination is a very safe procedure overall.

Follow-up

Given that second trimester MAs mostly occur under direct observation in an in-patient or day-patient setting, routine follow-up is not required. Prior to discharge, providers should

ensure complete passage of all pregnancy tissue, assess the patient's bleeding and address any contraceptive needs.

Contraception after First or Second Trimester MA

Addressing a woman's contraceptive needs after abortion should not be overlooked or postponed as ovulation can return as soon as 8 days after first trimester MA [92•]. Almost all methods of contraception can be initiated immediately at the time of the ingestion of mifepristone, with the exception of the IUD [93, 94]. IUD placement needs to be delayed until confirmation that a woman is no longer pregnant. IUD placement as soon as 5 days after mifepristone has been shown to be as safe as placement delayed to 3–6 weeks after mifepristone, without increased risk of expulsion and with lower lost-to-follow-up rates [95•, 96]. Women who are highly motivated to have an IUD might want to consider vacuum aspiration, as placement can occur at the same visit. However if a woman decides to proceed with MA, a shorter-acting method can be started immediately to "bridge" the time until an IUD can be placed.

To date there are no studies evaluating immediate IUD placement after second trimester MA. Data demonstrating the safety but higher expulsion risk of immediate postplacental IUD placement after term vaginal delivery can be extrapolated to apply to this population [97].

Current clinical recommendations support the initiation of all other methods of contraception at the time of mifepristone ingestion if the woman does not have a contraindication to use [3, 93]. Yet this recommendation is based on limited data. There is some theoretical concern that starting a hormonal-based method may impact MA efficacy, given that mifepristone is a progestin antagonist. A small pilot study of 20 women receiving the contraceptive implant on same day of mifepristone administration revealed that of the 16 who returned for follow-up, all had completed the abortion. At one year follow-up, 14 were satisfied with the timing of insertion and continued the implant [98•]. With regards to the potential decrease in contraceptive efficacy, mifepristone should no longer be present in the patient's serum in effective concentrations at the time of ovulation [99•]. These same concerns exist for depot medroxyprogesterone acetate injections, combined hormonal methods and progestin-only pills, but there are currently no data, and an ongoing clinical trial will hopefully provide more information [100].

Combined hormonal contraception in the form of pills, patch or vaginal ring, can be initiated immediately after first or second trimester MA if the patient does not have contraindications to estrogen [93]. Although both combined hormonal contraception and pregnancy are associated with slightly increased risks of thromboembolism, there has not been a clinically significant increase in thromboembolic events after first or second trimester abortion with combined hormonal contraception initiation [99•, 101].

Unfortunately, many states or insurance policies have restrictions preventing women from receiving contraception at the time of an abortion. Efforts to make all forms of contraception easily accessible to women to help reduce the risk of future unintended pregnancy should be continued.

Conclusion

Abortion is a common procedure that can be safely provided via medications or vacuum aspiration [1]. The availability of MA offers women a highly safe and effective option for terminating a pregnancy in the first or second trimester. A combination of mifepristone and misoprostol is the recommended regimen for both the first and second trimester of pregnancy, but doses, routes, and timing of administration vary with gestational age. For women wishing to delay fertility following an MA, the current recommendation is to start a contraceptive method immediately, except the IUD, which can be placed as soon as a woman is no longer pregnant. Further research should focus on optimal pain control for women undergoing MA at home, increasing gestational age limits for woman wanting to have an MA at home, reducing the number of clinic visits associated with MA, and immediate use of hormonal contraception and its impact on MA success.

Compliance with Ethics Guidelines

Conflict of Interest Eva Patil declares that she has no conflict of interest.

Alison Edelman reports that she is a consultant for the World Health Organization, Gynuity Health Projects, Genzyme, and Agile Therapeutics. Dr. Edelman is a Nexplanon trainer for Merck, an author for UptoDate (Royalties received), and has had research funding from the National Institute of Health, USAID and the Bill & Melinda Gates Foundation. These potential conflicts of interest have been reviewed and managed by OHSU.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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