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CHAPTER 9

Medical abortion in early pregnancy

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LEARNING POINTS

- The standard or classic regimen of mifepristone 600 mg followed 36 to 48 hours later by a prostaglandin analog, typically misoprostol 400 μg orally, is highly effective for abortion up to 49 days' gestation.
- Mifepristone can be used at a dose of 200 mg, instead of 600 mg, with equal efficacy and lower cost.
- When the misoprostol is used vaginally, the gestational age limit can be extended to 63 days and the medications can be administered as little as 6 to 8 hours apart or even simultaneously.
- Buccal and sublingual misoprostol also are effective when used at 24- to 48-hour intervals after mifepristone. These alternative routes appear to have more side effects than vaginal administration.
- Ultrasound examination 1 week after administering the medications is highly predictive of long-term success of the medical abortion procedure.
- Methotrexate and misoprostol can be used as an alternative regimen in women up to 49 days' gestation. The methotrexate does not appear to have immediate effect in the abortion process; rather, by rendering the pregnancy nonviable, methotrexate may serve as a backup for women who do not abort shortly after misoprostol administration.
- Misoprostol alone, in repeated doses, can be used for abortion where mifepristone is too expensive or unavailable. The recommended regimen for pregnancies up to 63 days' gestation is 800 μg administered vaginally every 3 to 24 hours for a maximum of three doses.

Introduction

The phrase *medical abortion* commonly refers to use of medications up to 63 days' gestation to effect abortion, although some regimens are effective beyond 63 days. Medical abortion allows a woman to have a safe, effective abortion without a surgical procedure. Since the early 1990s, millions of women in Europe, China, and North America have used mifepristone in combination with a prostaglandin analog for early abortion. However, in many regions of the world mifepristone is not available, prompting use of alternative regimens, including methotrexate in combination with misoprostol and misoprostol alone. This chapter reviews accumulated research on these medical methods of abortion and presents guidelines for their use in clinical practice.

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History of medical abortion

Early agents

Although using medications to induce abortion dates back centuries, effective medical regimens have emerged only in the last 50 years. In the early 1950s, Thiersch and colleagues [1] experimented with the folic acid antagonist, 4-aminopteroylglutamic acid (aminopterin) in mice, rats, and humans. Aminopterin was noted to induce embryonic demise and resorption in mice and rats during the first week of gestation. Oral aminopterin was then used to induce medically indicated abortions in women less than 3 months' gestation. Ten of 12 women aborted.

In the 1970s, natural prostaglandins such as PGE_2 and $PGF_{2\alpha}$ were found to induce early abortion effectively [2,3]. However, regimens that resulted in high efficacy also caused intolerable side effects, including nausea, vomiting, diarrhea, fever, and pain. Prostaglandin analogs developed in the mid-1970s acted more selectively on the myometrium, allowing use of lower doses to effect abortion, but their instability limited long-term use. By 1980, more stable analogs proved efficacious, including the vaginal suppository, gemeprost (16, 16-dimethyl-*trans*-Δ^2-PGE_1 methyl ester) [4–6], and the injectable analog, sulprostone (16-phenoxy-tetranor PGE_2

sulfonylamide) [7]. Gastrointestinal side effects were less severe with the analogs than with natural prostaglandins, but they still occurred commonly, thus limiting their clinical utility [4,8].

Modern era of medical abortion: Mifepristone

While investigating compounds that would block glucocorticoid receptors, a research team led by Dr. Etienne-Emile Baulieu recognized that some compounds also bound strongly to the similarly shaped progesterone receptor and blocked the action of progesterone. Further refinement led to the production of mifepristone, and clinical testing began in 1982. Initially, clinical investigators administered mifepristone alone for early abortion. For gestations up to 49 days, complete abortion occurred in approximately 60 to 80%, incomplete abortion in 6 to 30%, and continuing pregnancies in 7 to 40% [9–12]. Outcomes were not improved by varying the dose from 50 to 400 mg daily or by using single or divided doses over multiple days. At best, 80% of women treated with mifepristone alone in early pregnancy completely aborted within a few days. Adding small doses of a prostaglandin analog increased the complete abortion rate to almost 100% [10,13].

In 1988, France and China licensed mifepristone in combination with a prostaglandin analog for abortion up to 49 days' gestation. Subsequently, the United Kingdom and Sweden approved mifepristone for use up to 63 days' gestation. Beginning in late 1998 many other European countries approved mifepristone for sale and use, followed in 2001 by the USA.

Since the introduction of mifepristone in combination with a prostaglandin analog for medical abortion, research has continued with the goals of finding cost-effective regimens that maximize access and acceptability. Initial regimens used a single 600-mg oral dose of mifepristone followed by a prostaglandin analog. This dose of mifepristone is still used in many parts of the world, and it is the only dose included in the USA's Food and Drug Administration (FDA) labeling for mifepristone. Prostaglandin analogs used initially with mifepristone included gemeprost 1 mg vaginally or sulprostone 0.25 to 0.50 mg intramuscularly. Abortion occurred in 95 to 96% of women with pregnancies up to 49 days' gestation [14,15].

The single largest medical abortion trial included women through 49 days' gestation who received mifepristone with varying doses of gemeprost or sulprostone [15]. Three hundred centers enrolled 16,369 patients, and 15,709 women were included in the final analysis. Overall efficacy was 95.3% (95% CI 95.0, 95.6%), with no difference in treatment success rates by dose or type of prostaglandin analog. A small percentage (2.8%) of patients aborted after receiving mifepristone and before prostaglandin administration. Abortion occurred within 4 and 24 hours after the prostaglandin in 57 and 87% of subjects, respectively. Failures included continuing pregnancies (1.2%), incomplete abortions (2.8%), and curettage because of heavy vaginal bleeding (0.7%). Four serious cardiovascular complications (one myocardial infarction and three cases of severe hypotension) occurred with sulprostone injection. As a result of these and other reported cardiovascular events, use of sulprostone in medical abortion regimens ceased.

Effective regimens using mifepristone 600 mg and gemeprost 1 mg vaginally still resulted in considerable rates of vomiting (reported rates of 13 to 26%) [16–18] and diarrhea (reported rates of 10 to 13%) [16,17]. Using a lower (0.5 mg) dose of gemeprost approximately 48 hours after 600 mg of mifepristone resulted in similar efficacy and side effect rates [19]. In 391 women up to 63 days' gestation 97% (95% CI 95, 99%) aborted, with no difference by gestational age. Although gemeprost is the prostaglandin analog approved for use with mifepristone for medical abortion up to 63 days' gestation in the United Kingdom, Sweden, and Norway, it has several disadvantages compared to misoprostol. Gemeprost is more expensive and requires refrigeration, important drawbacks in developing countries. Moreover, clinical trials have suggested that mifepristone followed by vaginal misoprostol demonstrates superior efficacy, lower rates of continuing pregnancy, and similar side effects as compared to mifepristone with gemeprost [20]. These aspects have led to the gradual substitution of misoprostol for gemeprost over the last few years; today, misoprostol is the most commonly used prostaglandin analog in regimens for medical abortion.

Although mifepristone is approved in more than 30 countries worldwide, most women live in countries where mifepristone is not available or not widely affordable or where access to legal abortion is lacking [21]. Even where mifepristone is approved for medical abortion, usage patterns may vary among countries or within different regions of the same country. As of 2000, for example, more than half of abortions within approved gestational limits were accomplished using a mifepristone regimen in France (56%), Scotland (61%), and Sweden (51%) compared to only 18% in England and Wales [22]. In various regions of Sweden, use of mifepristone for abortion ranges from 10 to 60% of eligible abortions [23]. Similar variations exist throughout the USA, where medical abortion use by state varies from 0 to 32% of all abortions [24]. In 2005 medical abortion accounted for 13% of all abortions and 22% of abortions before 9 weeks' gestation [25] (Chapter 3). Danco Laboratories, LLC, the company that supplies mifepristone in the USA, estimates that more than 1 million women in the USA used the product for abortion by the end of 2008 (Danco Laboratories, LLC, personal communication).

Further research has revealed other medical uses for mifepristone. In Europe, subsequently approved indications include labor-induction abortion, labor induction for fetal demise, and cervical ripening. Additionally, mifepristone is

used in China for emergency contraception. Other potential uses include treatment of symptomatic leiomyomata uteri, endometriosis, Cushing's syndrome, contraception, depression, breast cancer, and glaucoma.

Modern era of medical abortion: Nonmifepristone regimens

Because mifepristone was not available in most countries, investigators searched for alternative means to provide a medical abortion. With the publication of studies demonstrating the effectiveness of low-dose methotrexate for treatment of extrauterine pregnancy [26], this agent emerged as a potential candidate. In January 1993, researchers in the USA started clinical trials using low-dose methotrexate and misoprostol for early abortion [27], leading to the clinical protocols in use today. However, in many developing countries, even access to methotrexate is limited.

Whereas past studies evaluating prostaglandins and prostaglandin analogs alone for medical abortion did not result in clinically useful regimens, the emergence of misoprostol as an inexpensive agent that was stable at room temperature reignited interest in such regimens. Misoprostol was initially evaluated as a single agent for use in the management of early pregnancy failure and abortion beyond 11 weeks' gestation. Subsequent research indicated that vaginal administration of misoprostol 800 μg repeated up to three times at intervals ranging from 3 to 24 hours effected complete abortion in 85 to 90% of women up to 9 weeks' gestation. Sublingual administration at 3-hour intervals had similar efficacy but with more frequent side effects. As expected, oral administration is less effective [28].

Although not as effective as combined regimens, misoprostol alone, with repeated doses if necessary, does provide an important medical abortion option for women in many countries. In countries where mifepristone is not available, misoprostol-alone regimens are now widely used and have been shown to reduce mortality and morbidity associated with illegal unsafe abortion [29,30] (Chapters 2 and 22).

Agents

Mifepristone

Overview

Progesterone, as its names suggests ("pro-gestation"), is fundamentally important for sustaining an early pregnancy. Withdrawal of progesterone support during early human pregnancy results in uterine contractions with expulsion of the embryo by a prostaglandin-mediated mechanism [31]. Inhibition of progesterone effects is accomplished by preventing its synthesis or blocking its action at the receptor. Mifepristone (Figure 9.1), a derivative of norethindrone, binds to the progesterone receptor with an affinity greater

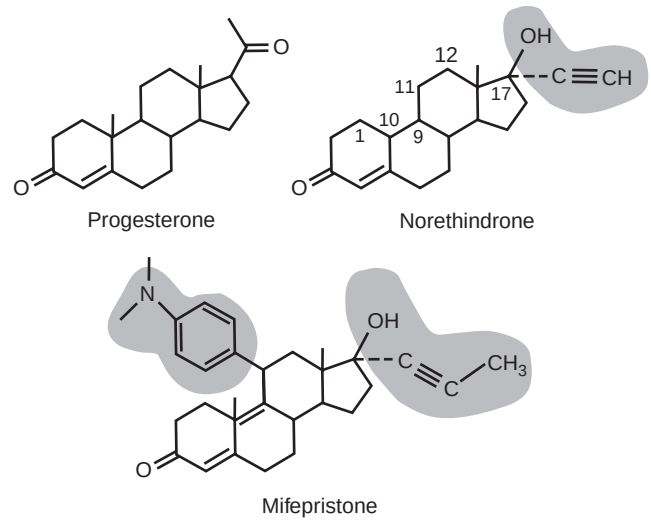

Figure 9.1 Structural formulas of mifepristone, norethindrone, and progesterone. To create mifepristone from norethindrone, a long side-chain is added at the 17-carbon position, which makes it bind very tightly to the progesterone receptor, and a bulky side-chain is added at the 11-carbon position, rendering it inactive.

than progesterone itself without activating the receptor, thereby acting as an "antiprogestin"[32].

Mifepristone has several effects on the uterus and cervix during early pregnancy:

- Mifepristone induces uterine contractility directly by reversing progesterone-induced inhibition in gap junction formation [33]. In addition, contractility is indirectly affected by a resultant increase in myometrial sensitivity to prostaglandins [34].
- Mifepristone alters the endometrium directly by affecting the capillary endothelial cells of the decidua; it has no direct effect on the trophoblast [35,36]. Decidual necrosis results in separation of the trophoblast from the decidua, causing bleeding and a decrease in human chorionic gonadotropin (hCG) secretion into the maternal system. The decidual action also increases prostaglandin release [37].
- Mifepristone softens the cervix to allow expulsion.

Notably, mifepristone is not effective as a primary treatment for extrauterine pregnancy [38], most likely because of a lack of progesterone receptor expression in fallopian tubes containing an ectopic pregnancy [39].

Human studies have suggested that uterine contractility does not increase until 24 to 36 hours after mifepristone administration but is preceded by an increase in myometrial sensitivity to prostaglandins [34]. At this point, the myometrium is five times more sensitive to the stimulatory effects of exogenous prostaglandins. However, recent studies have shown high efficacy when vaginal misoprostol is administered less than 15 minutes after mifepristone [40]. The effectiveness of such a regimen cannot be attributed

to the actions of the misoprostol, as misoprostol alone has a much lower efficacy. Accordingly, these studies suggest that some or all of these actions occur sooner or that the effects of mifepristone that are important and necessary for its abortifacient activity remain incompletely understood.

Pharmacokinetics

When administered orally, mifepristone is easily absorbed, reaching peak serum concentrations in pregnant and nonpregnant women within 2 hours regardless of dose [41]. The pharmacokinetics of mifepristone differ for daily doses less than 100 mg than for higher doses; at doses of 100 mg or more, serum levels are similar [42–44]. Comparable peak serum concentrations of 2.0 to 2.5 μg/ml occur in women given 100 mg, 400 mg, 600 mg, or 800 mg of mifepristone [45]. The nonlinear pharmacokinetics may be due to saturation of a specific transport protein for mifepristone, serum alpha-1-acid glycoprotein; this protein is saturated at doses of 100 mg or more [46]. These data indicate that single doses as low as 100 mg are likely to be as effective as 600 mg. The half-life of mifepristone is approximately 24 to 29 hours [44,45]. Because mifepristone without a prostaglandin failed to induce abortion consistently, researchers sought to determine if failure was related to serum concentrations of mifepristone and its metabolites. In women receiving a single 600-mg dose of mifepristone, serum levels of mifepristone or its metabolites did not differ between those who did and did not abort [47]. Therefore, increasing the dose to more than 600 mg is unlikely to result in a better outcome.

Methotrexate

Overview

Methotrexate blocks the enzyme dihydrofolate reductase, thereby inhibiting the production of reduced folates required for DNA synthesis. Methotrexate primarily affects rapidly dividing cells. Medical conditions in which rapid cell division occurs include cancers, autoimmune diseases, and pregnancy. More than 50 years ago, the US FDA approved methotrexate to treat certain neoplastic diseases, rheumatoid arthritis, and psoriasis. Since 1982, multiple investigators have used various multidose regimens of methotrexate off-label to treat ectopic pregnancy, with efficacy rates in the 90 to 95% range (Chapter 18). Because methotrexate should have similar effects on both extrauterine and intrauterine trophoblast, its potential for abortion was obvious.

In contrast to the high-dose regimens required to treat cancer, low doses of methotrexate suffice for other medical conditions, including early abortion and treatment of unruptured ectopic pregnancy. This distinction is important, because toxicity is dose-dependent. High-dose versus low-dose, though, is not actually a comparison of absolute quantity administered at one time, but the total dose administered over a given period of time (area under the curve). Thus, a patient given a single 85-mg injection of methotrexate is receiving low-dose therapy compared to a person who receives a 50-mg injection 5 days in a row.

High-dose methotrexate can affect the lining of the gastrointestinal tract, bone marrow, and pulmonary interstitium; with very high doses, renal toxicity and alopecia also can occur. However, with the low doses used for ectopic pregnancy or abortion, side effects are usually limited to mild gastrointestinal problems like nausea, vomiting, or diarrhea. Women treated with methotrexate for gestational trophoblastic tumors have normal future reproductive function [48]. After low-dose methotrexate treatment for ectopic pregnancy, menses return normally and pregnancy rates are similar to those achieved by traditional surgical treatment [26]. Thus, methotrexate has no effect on future fertility and does not increase the risk of anomalies in subsequent pregnancies.

Pharmacokinetics

Very limited pharmacokinetic information is available for methotrexate in pregnant women. In 10 women up to 49 days' gestation who received methotrexate 50 mg/m^2 intramuscularly to induce abortion, serum levels peaked within 1 to 2 hours, which is similar to results in nonpregnant subjects [49]. The mean peak serum concentration was 4.4 ± 0.9 μmol/l and did not exceed 5.0 μmol/l at 24 hours in any patient. Serum levels were nondetectable within 48 hours. The renal clearance rate was the same as that for men and nonpregnant women receiving methotrexate in lower doses for rheumatoid arthritis or asthma.

Misoprostol

Overview

Misoprostol (11α, 13E, 16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oic acid methyl ester) is a synthetic prostaglandin E_1 analog developed in 1973 for the treatment and prevention of gastric ulcers. Misoprostol tablets are produced primarily for oral use in doses of 100 μg and 200 μg. Treatment and prevention of gastric ulcer is still the only licensed indication for misoprostol, with the exception of Gymiso® in France (200 μg tablets for abortion) and a 25 μg vaginal suppository approved in Brazil and Egypt for induction of labor. Despite the lack of an approved indication for use alone in medical abortion, misoprostol is specifically mentioned as the prostaglandin analog of choice in the marketing authorization for mifepristone in the USA and European countries and, together with gemeprost, in the United Kingdom, Sweden, and Norway.

Misoprostol has become an important drug in obstetrics and gynecology because of its uterotonic and cervical priming actions. Misoprostol has several advantages over other prostaglandins on the market: it is inexpensive, has no effect

on the bronchi or blood vessels, and can be stored at room temperature for many years; moreover, the tablets for oral use are also effective when used vaginally, sublingually, or rectally. Because mifepristone is more costly and less available, the use of misoprostol alone for medical abortion has become common through both medical and informal routes of provision [50]. However, the misoprostol-alone regimens are less effective, require higher doses of misoprostol, and thus result in more side effects.

Pharmacokinetics

Misoprostol is rapidly and extensively absorbed from the gastrointestinal tract and undergoes rapid first-pass metabolism (de-esterification) to form the free acid, which is responsible for its clinical activity. Unlike the parent compound, misoprostol acid is detectable in plasma [51,52]. Taking misoprostol orally with food diminishes maximum plasma concentrations of misoprostol acid and concomitant use of antacid reduces its total availability [53].

The pharmacokinetics of misoprostol differ by route of administration. Following a single dose of 400 μg oral misoprostol, the plasma misoprostol level increases rapidly and peaks at about 30 minutes; the plasma level then declines rapidly by 120 minutes [54–57]. After vaginal administration, the plasma concentration rises gradually, reaching a maximum after 70 to 80 minutes; it then slowly declines, with levels detectable up to 6 hours after administration. Compared to the oral route, the peak plasma concentration following vaginal administration is lower (Figure 9.2) but the "area under the curve" (AUC), or total bioavailability, is significantly greater [54,55,58]. Whereas initial findings of tablet remnants hours after vaginal administration led clinicians to assume that absorption is variable and incomplete, the remnants likely reflect the lack of complete breakdown of the tablet fillers with vaginal administration rather than any variance in absorption. Attempts have been made to improve the absorption of vaginal misoprostol. Athough the addition of water to the misoprostol tablets is a common practice, it does not significantly improve the bioavailability of vaginal misoprostol [55].

Buccal and sublingual routes of misoprostol administration have also been investigated for medical abortion. With both routes, the tablets are usually swallowed after 30 minutes, so a small amount of gastric absorption may occur as well. Systemic bioavailability as measured by the AUC is highest following sublingual use [55,59]. With buccal use, the shape of the absorption curve is similar to that of the vaginal route; however, the plasma drug levels attained are lower, and the AUC is only half that observed after vaginal administration [57]. The AUC for sublingual misoprostol is four times that seen after buccal administration [60]. However, measures of uterine contractility comparing buccal or sublingual administration to the vaginal route are quite similar [61].

Medical abortion regimens

Mifepristone regimens

Standard ("classic") regimen

The standard or "classic" regimen derives from early studies of mifepristone and a prostaglandin analog adapted for the use of misoprostol in place of earlier analogs. The

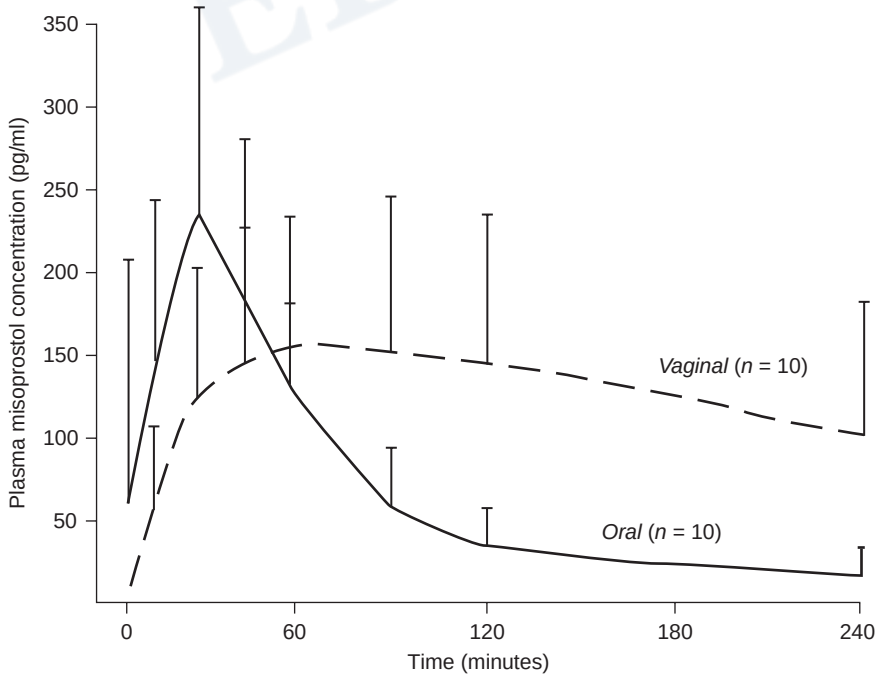

Figure 9.2 Mean plasma concentrations of misoprostol acid over time with oral (solid line) and vaginal (dotted line) administration. Arrow bars represent one standard deviation [54]. (Reprinted with permission from the American College of Obstetricians and Gynecologists.)

first large-scale study using the mifepristone/misoprostol combination involved 873 women up to 49 days' gestation [62]. Peyron and colleagues described two consecutive studies in which all women received mifepristone 600 mg orally followed 48 hours later by a single oral dose of misoprostol 400 μg. Women in the second study were also eligible to receive an additional 200 μg of misoprostol orally if abortion had not occurred within 4 hours. Overall 4% of women aborted solely from the mifepristone. Complete abortion occurred in 96.9% (95% CI 94.1, 97.7%) of the 488 women treated in the first study and in 98.7% (95% CI 96.8, 99.5%) of the 385 subjects in the second study, a nonsignificant difference. The abortion rates in the first 4 hours after misoprostol administration were 61 and 69% in the two studies, respectively, implying that the difference in overall efficacy was not necessarily a factor of the second dose. One woman (in group 1) required a transfusion. Nausea, vomiting, and diarrhea occurred after the misoprostol in approximately 40%, 15%, and 10% of women, respectively.

The use of mifepristone and oral misoprostol is approved in France, the USA, and other countries through 49 days' gestation. The efficacy of this regimen falls significantly thereafter, as well demonstrated by the first large-scale US clinical trial, which was performed by the Population Council in women up to 63 days' gestation [63]. Women at 17 clinical sites received mifepristone 600 mg orally and returned 2 days later to receive misoprostol 400 μg orally. The women stayed in the clinic for a minimum of 4 hours of observation then returned 12 days later for a final visit, at which time a physical or ultrasound examination was performed to confirm complete expulsion.

For the 2,005 women included in the final analysis of efficacy, failure rates at 49 days' or less, 50 to 56 days', and 57 to 63 days' gestation were 7.9%, 17.0%, and 22.5%, respectively. In pregnancies up to 49 days' gestation, the rate of ongoing pregnancy was comparable to previously published trials (approximately 1%); however, the rates at 50 to 56 days' and 57 to 63 days' gestation were higher than European studies (3.7 and 9.0%, respectively).

The time of expulsion was known for 1,468 subjects; 49% aborted within 4 hours and 75% within 24 hours after misoprostol administration. The median duration of bleeding was 13 days in the group up to 49 days' gestation and 15 days in women with more advanced gestations; 9% of women had bleeding that lasted more than 30 days. Four women received blood transfusions including one subject at 49 days' gestation or less, one at 57 to 63 days' gestation, and two subjects at 50 to 60 days' gestation.

The practical clinical application of this standard regimen requires three visits. The first visit involves patient education and consent, gestational age determination, and treatment. In some regions, specific counseling or consent must take place well in advance of treatment as mandated by law. Gestational age is determined in different ways depending on local standards and resources. Some practitioners use the woman's menstrual history and pelvic examination primarily, with sonography reserved only for questionable cases; others, especially in the USA, use sonography routinely for all patients. Similarly, some providers obtain hemoglobin or hematocrit measurements only in women at risk for anemia because of poor health, poor nutrition, or a history of bleeding, and others obtain such measurements in all women. Treatment with mifepristone is 600 mg (three 200-mg pills) taken orally in front of the provider.

The second visit occurs 2 days later, approximately 36 to 48 hours after the mifepristone. If the woman gives a history compatible with abortion, she typically is examined to see if she has expelled the pregnancy, which occurs in less than 5% of women. Women who are still pregnant receive misoprostol 400 μg (two 200-μg tablets) orally and stay at the center for a maximum of 4 hours. Women receive pain medication as needed and may leave after expulsion of the pregnancy is confirmed clinically. If 4 hours pass without apparent expulsion, an examination is performed before women leave because sometimes the expelled gestational sac is in the vagina. The third visit occurs approximately 2 weeks later. Women without confirmed expulsion undergo sonographic examination. Women with a persistent gestational sac, whether or not gestational cardiac activity is present, are typically offered vacuum aspiration.

Slight variations of the standard regimen include not requiring that women stay in the clinic following misoprostol treatment and administering additional doses of misoprostol at the clinic. The former adaptation followed agency approval in the USA, with the US FDA not mandating a 4-hour observation period. Additional misoprostol doses have been studied systematically without evidence of benefit. In addition to the work of Peyron and Aubeny et al [62] discussed previously, Aubeny and Peyron et al. [64] performed a multicenter trial that included 1,108 women up to 63 days' gestation who were treated with this regimen but were also offered an additional 200 μg of misoprostol orally. Complete abortion rates were highest at lower gestational age: 97.6% up to 42 days' gestation, 94.8% from 42 to 49 days' gestation, 93.4% from 50 to 56 days' gestation, and 86.8% from 57 to 63 days' gestation. Similarly, continuing pregnancy rates increased with advancing gestational age: 0.8%, 1.4%, 1.6%, and 5.1%, respectively. Overall, 61.6% of women had not expelled the pregnancy within 3 hours of misoprostol administration and received a second dose. The group of women through 49 days' gestation was compared with a historical cohort of women who received only a single dose of misoprostol with no significant improvement in the expulsion rate using the repeat dose. A randomized, blinded study in India evaluated a routine second dose of misoprostol 3 hours later as compared to placebo [65] in women up to 56 days' gestation. The study was significantly underpowered so an apparent trend toward a benefit did not show

statistical significance. Treatment success rates in the single-dose and multiple-dose groups were 86 and 92%, respectively ($p = 0.11$). Continuing pregnancy rates, though, were significantly different (7% vs. 1%, $p = 0.005$). The gestational ages of the continuing pregnancies were not described. This study, in combination with those mentioned previously, fails to support any benefit of the routine use of a second misoprostol dose in women up to 49 days' gestation using the standard mifepristone-misoprostol regimen.

Alternative evidence-based regimens

Despite the early acceptance in France and most other countries of the standard regimen in women up to 49 days' gestation [38], alternative regimens using these agents were sought that would cause fewer side effects, be less expensive, or be more acceptable to providers and patients. Studies have led to lower doses of mifepristone, non-oral dosing of misoprostol, home administration of the misoprostol, earlier follow-up, and altering the timing of the misoprostol dose following mifepristone.

Lower doses of mifepristone

As expected based on the pharmacokinetics of mifepristone, lower doses of mifepristone are equally as effective as the 600-mg dose when combined with either gemeprost or misoprostol [18,66,67]. Because mifepristone is the more expensive of the medications, lower-dose regimens are more economical. In 1992, Thong and Baird [68] first reported using mifepristone 200 mg followed 48 hours later by misoprostol 600 μg orally in 100 women up to 56 days' gestation. Overall, the regimen was 92% effective, with 79% of women aborting within 4 hours of misoprostol administration. A randomized trial performed by the World Health Organization (WHO) [67] included women up to 63 days' gestation who received either mifepristone 200 mg ($n = 792$) or 600 mg ($n = 797$) followed 48 hours later by misoprostol 400 μg orally. Complete abortion rates were similar for both groups (89 and 88%, respectively) and were gestational age dependent: 92% up to 42 days, 89% at 43 to 49 days, 87% at 50 to 56 days, and 80% after 56 days. Rates of side effects were comparable in the groups. Subsequent to these trials, most large studies and commonly used clinical protocols have employed 200 mg of mifepristone for medical abortion. Efficacy is still maintained when mifepristone 200 mg is used with misoprostol 400 μg orally through 49 days' gestation [69]. Additionally, in 2007 the 200-mg mifepristone dose, when used with a vaginal prostaglandin analog, received regulatory approval by the European Medicines Agency, affecting the entire European Union.

Alternate routes for misoprostol

Administering misoprostol vaginally, as compared to the standard oral route, allows the effective use of mifepristone regimens after 49 days' gestation (Table 9.1). In general, efficacy rates are approximately 95 to 98% up to 49 days' gestation, 93 to 98% from 50 to 56 days, and 92 to 98% from 57 to 63 days. Despite the success with vaginal dosing, studies suggest that women prefer an oral route [70]. Both buccal and sublingual regimens have been investigated with success, although the magnitude of the literature is much smaller than that for vaginal misoprostol. Additionally, use after 63 days' gestation has been investigated.

Use of buccal misoprostol appears equivalent to vaginal misoprostol. Middleton and colleagues [71] randomized 442 women with gestations of 56 days or less to 200 mg mifepristone orally followed 1 to 2 days later by 800 μg misoprostol given by the vaginal or buccal route. Buccal administration consisted of allowing the tablets to dissolve for 30 minutes after which the remaining fragments were swallowed. The complete abortion rate was 95% in the buccal group and 93% in the vaginal group ($p = 0.51$). With the exception of diarrhea, which occurred more frequently in the buccal group (36% vs. 24%, $p = 0.006$), the side effect profiles were similar. Overall satisfaction rates were high in both groups (92% buccal vs. 95% vaginal, $p = 0.18$). When women were queried regarding their preferences for the route of administration, 16% of women in the buccal group would have preferred vaginal administration compared with 11% in the vaginal group who would have preferred buccal. A recent study confirmed this high efficacy with use of mifepristone and buccal misoprostol through 63 days' gestation [72].

Three studies have been published that combine mifepristone and sublingual misoprostol. Hamoda and colleagues [73] randomized 340 women up to 13 weeks' gestation to receive mifepristone 200 mg followed by misoprostol 600 μg sublingually ($n = 171$) or 800 μg vaginally ($n = 169$) 36 to 48 hours later. Most (62%) subjects were beyond 63 days' gestation. Subjects were admitted for observation during misoprostol treatment. In women up to 9 weeks' gestation, an additional dose of misoprostol 400 μg was administered by the same route 3 hours later. Women over 9 weeks' gestation received additional misoprostol 400 μg if the pregnancy had not passed within 3 more hours. Overall efficacy in both groups was the same (97 to 98%); however, women who received sublingual misoprostol experienced significantly more diarrhea (71% vs. 52%), shivering (84% vs. 64%), and unpleasant taste (71% vs. 32%).

Singh and colleagues [74] reported a pilot study of 40 women up to 8 weeks' gestation who received mifepristone 200 mg followed 24 hours later by three doses of misoprostol 200 μg sublingually administered 6 hours apart. All of the women had complete abortions. Another recent report from Taiwan included 356 women up to 49 days' gestation treated with mifepristone 200 mg followed 48 hours later by misoprostol 600 μg sublingually [75]. This study also demonstrated high efficacy, with complete abortion in 98% of participants.

Table 9.1 Outcome of treatment with mifepristone 200 mg followed by misoprostol 800 μg vaginally by gestational age.

		≤49 Days			50–56 Days			57–63 Days		
Primary Author	Interval between Mifepristone and Misoprostol	Number	Complete Abortion (%)	Continuing Pregnancy (%)	Number	Complete Abortion (%)	Continuing Pregnancy (%)	Number	Complete Abortion (%)	Continuing Pregnancy (%)
Ashok (1998) [106]	36–48 hours	928	98.5	0.2	1,072[a]	96.7[a]	0.8[a]			
Schaff (1999) [79]	48 hours	660	97.4	0.3	273	96.3	1.1			
Schaff (2000) [80]	48 hours	578	97.7	0.2	251	96.8	0.4	308	96.0	1.0
Bartley (2001) [20]	48 hours	232	99.6	0	164	98.2	0	55	96.5	1.8
Schaff (2002) [122]	36–48 hours	349	98.2	0.6	113	98.2	0	60	93.3	0
Tang (2003) [147]	48 hours	26	96.2	0	86	93.1	2.7			
von Hertzen (2003) [148]	36–48 hours	223	95.1	–	242	93.4	0.4[b]	268	92.2	0
	36–48 hours[c]	240	94.6	–	246	93.1	0.2[b]	254	96.5	0
Creinin (2004) [88]	6–8 hours	245	97.1	0	154	94.2	0	126	95.2	0.8
	23–25 hours	258	98.4	0	157	97.5	0.6	116	98.3	0
Shannon (2006) [149][d]	24–48 hours	240	95.4	0	59	90.8	0			
Creinin (2007) [40]	<15 minutes	266	95.5	0.4	159	94.3	1.3	129	95.3	0.8
	23–25 hours	229	98.3	0.4	172	95.3	0	145	96.6	0

[a] Women 50–63 days' gestation.

[b] Continuing pregnancy rate for combined groups up to 56 days' gestation.

[c] Received misoprostol 400 μg orally twice daily for 1 week after vaginal misoprostol.

[d] Subjects could self-administer a second dose after 24 hours if they had little bleeding.

One of the primary advantages of non-oral misoprostol dosing is the continued efficacy of these regimens to 63 days' gestation and beyond. Limited trials have demonstrated continued efficacy of mifepristone and misoprostol between 9 and 13 weeks' gestation. In addition to the experience with vaginal and sublingual misoprostol previously described [73], multiple studies and case series have reported the successful use of mifepristone and vaginal misoprostol after 63 days' gestation. Regimens typically include additional doses of misoprostol 400 μg orally, vaginally, or sublingually every 3 hours as deemed necessary by the treating clinician. Unlike regimens up to 9 weeks' gestation, all of these studies have kept women in the office or hospital for observation during treatment. Vacuum aspiration is reported in approximately 5 to 10% of women overall, with higher rates with advancing gestation [76–78].

Home administration of misoprostol

Although initial protocols for use of mifepristone and a prostaglandin analog included in-office observation, home use of the prostaglandin analog with self-administration has become the standard of care in much of the world. Most trials using mifepristone and misoprostol in North America include home administration, and even the regulatory labeling for mifepristone in the USA does not require that the patient remain under observation after using the prostaglandin analog. Two large studies specifically evaluated adverse events in the hours after misoprostol during home use; only four (0.1%) women were noted to have emergencies [79,80]. Two of these women presented for an emergent aspiration for heavy bleeding; neither required a blood transfusion. One patient had a vasovagal reaction, and one woman had a syncopal episode while bleeding and fell and broke her nose. Only the latter occurrence (1 out of approximately 4,500 women) would potentially have been avoided with in-office observation. A recent pilot investigation of home use of misoprostol from Sweden and France demonstrated that women in those countries also manage well without being observed in the clinic. Of the 130 women using oral misoprostol at home, 98% reported no trouble with the regimen and 98% would use it at home again for a next abortion [81,82]. In 2004, Sweden changed its regulatory guidelines to allow medical abortion with mifepristone and home use of misoprostol up to 63 days' gestation.

Earlier follow-up

Women receiving the standard regimen are scheduled for follow-up approximately 2 weeks after initiating treatment. By this time, a woman who has successfully aborted will likely have light to no bleeding, a lack of pregnancy symptoms, and a small uterus on examination. Sonography is commonly reserved for situations where the outcome cannot be determined by a simple history and physical examination.

Multiple clinical trials have included earlier follow-up with the use of routine sonography. Although routine use of sonography could potentially increase cost, it does allow for earlier determination of success with high predictability. Studies using sonography have included follow-up as early as 24 hours posttreatment. To determine success, most investigators simply look for the absence of a gestational sac whereas others also use endometrial thickness. Although endometrial thickness can be slightly greater in women who ultimately need a uterine evacuation procedure, studies of women receiving medical treatment for abortion or early pregnancy failure have shown that the measurement has poor positive predictive value and no clinical utility [83–87].

Only a few recent studies have included routine follow-up beyond 2 weeks [40,88–90]. In two studies by Creinin and colleagues, the investigators evaluated women 1 week after treatment using transvaginal sonography and continued to follow the subjects for a total of 5 weeks. In these studies, 78% [88] and 88% [40] of subjects who had not already had a vacuum aspiration were contacted 5 weeks after initiating treatment. A total of 14 (1.7%) and 13 (1.3%) women required an aspiration procedure during the prolonged follow-up. Thus, women in these trials were very unlikely to need further intervention, demonstrating the high predictability of sonography at 1 week.

Time interval between mifepristone and misoprostol

In the past decade much research has focused on the time interval between mifepristone and misoprostol administration. Acceptability is higher with shorter time intervals [91]. The combination of mifepristone with oral misoprostol at an interval of less than 36 to 48 hours is not effective. Creinin et al [92] randomized 86 women taking the standard regimen to use the misoprostol 24 or 48 hours after the mifepristone. Expulsion at 24 hours was evaluated for potential efficacy of this new regimen, with complete abortion rates of 50% and 91%, respectively (RR = 0.55 [95% CI 0.42, 0.73]).

Regimens with non-oral misoprostol routes, however, allow for high efficacy with a shorter interval. Schaff et al [91] reported a multicenter randomized trial in 2,295 women up to 56 days' gestation who self-administered misoprostol 800 μg vaginally 24, 48, or 72 hours after taking mifepristone 200 mg orally. The misoprostol dose was repeated at a 1-week follow-up visit if vaginal ultrasound examination did not confirm expulsion. Complete medical abortion occurred in 98% (95% CI 97, 99%), 98% (95% CI 97, 99%), and 96% (95% CI 95, 97%), respectively. The time waiting for expulsion was acceptable in 86%, 79%, and 76%, respectively ($p = 0.001$). In a later trial, the same investigative team showed continued high efficacy of the combination of mifepristone and misoprostol 800 μg vaginally 24 hours later up to 63 days' gestation [70].

A stepwise progression of studies has demonstrated that vaginal misoprostol can be used simultaneously with

the mifepristone. First, Creinin et al [88] performed a multicenter, randomized trial of 1,080 women up to 63 days' gestation who received the misoprostol either 6 to 8 hours ($n = 540$) or 23 to 25 hours ($n = 540$) following the mifepristone. Complete abortion rates were equivalent (96 and 98%, respectively). Continuing pregnancy rates were 0.4 and 0.1%, respectively. Surprisingly, side effects after mifepristone administration were significantly more common in the women who received misoprostol 23 to 25 hours later. Additionally, nausea, vomiting, and heavy bleeding were significantly greater after misoprostol treatment in this group. Pain and subject acceptability were similar between groups.

Investigators in the UK attempted a similar comparative multicenter trial, randomizing 450 women up to 63 days' gestation to receive the misoprostol either 6 hours ($n = 225$) or 36 to 48 hours ($n = 225$) following the mifepristone [90]. Women in the 6-hour group returned for the misoprostol and then went home. Women in the 36- to 48-hour group returned for the misoprostol and stayed in the clinic for 4 to 6 hours. Complete abortion rates were 89 and 96%, respectively (RR = 0.92 [95% CI 0.84, 0.98]). The results of this smaller study are quite discrepant from those of the US trial. More women were considered to have incomplete abortions in the UK trial (4% vs. 2%), and more women had vacuum aspirations for persistent gestational sacs (4% vs. 0.6%). Most likely, the differences in protocol led to higher use of aspiration in the UK: specifically, conducting the follow-up sooner, requiring women to stay in the clinic longer if they wanted a repeat dose (which encouraged choice of a quicker aspiration procedure), and using incorrect ultrasound criteria to define incomplete abortion.

Additional work from the USA indicates that the timing can be decreased further when using misoprostol vaginally. Creinin et al [40] performed a multicenter, randomized trial of 1,128 women up to 63 days' gestation who received the misoprostol either within 15 minutes of the mifepristone administration ($n = 567$) or 23 to 25 hours ($n = 561$) following the mifepristone. Complete abortion rates were statistically equivalent (95 and 97%, respectively). Continuing pregnancy rates were 0.7% and 0.2%, respectively. Women who used simultaneous dosing had a lower likelihood of expulsion with a single dose of misoprostol as compared to the 23- to 25-hour interval (91 vs. 94% $p = 0.10$ for noninferiority). However, simultaneous use of misoprostol has a practical advantage in that the misoprostol cannot be improperly placed or lost.

Studies using buccal and sublingual misoprostol similarly have demonstrated that a 24-hour interval can be used with high success [74,78]. However, unlike with vaginal misoprostol, the combination of mifepristone and buccal misoprostol is not effective when the two are used simultaneously [89].

Methotrexate regimens

Initial clinical trials of methotrexate and misoprostol for early abortion began in 1993, 11 years after the start of human testing on mifepristone [27]. The encouraging results led to larger trials that have investigated a longer interval between methotrexate and misoprostol administration, the effects of moistening the misoprostol, and use of oral methotrexate (Table 9.2).

In general, it appears that the methotrexate has little effect as an abortifacient, as abortion rates in the short term are similar to those of misoprostol alone. Rather the methotrexate acts to create a nonviable gestation should the misoprostol not work. A randomized trial in women up to 7 weeks' gestation supports this point. Wiebe and colleagues [93] reported in brief about a randomized comparison of the combined regimen of methotrexate 50 mg/m^2 intramuscularly followed 72 hours later by misoprostol 800 μg vaginally ($n = 149$) and a misoprostol-only regimen that combined misoprostol 400 μg sublingually and 400 μg vaginally ($n = 149$). Efficacy in both groups following one treatment was about 60%. A recent review counters this finding. Aldrich [94] reported a large study of sequential cohorts, using first misoprostol alone and subsequently methotrexate and vaginal or buccal misoprostol. Success rates were 77% for misoprostol alone and 82 to 84% for methotrexate regimens. The nature of the review, however, limits its utility.

As with mifepristone regimens, recent studies have evaluated methotrexate combined with nonvaginal misoprostol. Wiebe and Trouton [95] compared buccal and vaginal misoprostol used after intramuscular methotrexate 50 mg/m^2. Women with gestations up to 49 days were randomized to 600 μg of misoprostol administered vaginally or buccally 3 to 6 days after receiving methotrexate. Women in the buccal group were instructed to allow the tablets to dissolve for 1 hour and then to spit out any remaining fragments. The overall complete abortion rate 8 days after misoprostol administration was statistically higher in the vaginal misoprostol group (67.5% vs. 53.5%, $p = 0.01$); the acceptability was similar in both groups, as was the eventual need for surgical abortion, likely reflecting the efficacy of methotrexate. The efficacy rate in this study is lower than that previously reported for methotrexate used with 800 μg of vaginal misoprostol (Table 9.2), suggesting that the lower dose of misoprostol rather than the route of administration may have contributed to the findings. In addition, expelling the remaining fragments of misoprostol after 1 hour may have lowered the overall dose of misoprostol in the buccal group, although serum concentrations were not determined.

Comparison to mifepristone regimens

A randomized trial in Canada compared the efficacy and side effects of mifepristone 600 mg followed 36 to 48 hours later by misoprostol 400 μg orally ($n = 518$) and methotrexate 50 mg/m^2 intramuscularly followed 4 to 6 days later

Table 9.2 Selected studies of medical abortion using methotrexate (MTX) and vaginal misoprostol (MIS).

Primary Author	N	Gestational Age (Days)	MTX Dose, Route of Administration	MIS Dose[a]	Interval between MTX and MIS (days)	Repeat Dose of MIS (days after MIS dose)[b]	Follow-up Period (days after MTX)	Overall Success (%)
Hausknecht (1995) [150]	178	≤63	50 mg/m^2 IM	800 μg	5 to 7	7	14	96.1
Creinin (1995) [151]	46	≤56	50 mg/m^2 IM	800 μg	3	4	56	82.6
	40				7	1		97.5
Creinin (1996) [115]	300	≤56	50 mg/m^2 IM	800 μg	7	7	14/35	69.7/91.7
Creinin (1997) [152]	100	≤49	75 mg IM	800 μg	5 to 6	7	14/44	77.8/94.9
Creinin (1997) [116]	299	≤49	50 mg PO	800 μg	5 to 6	7	14/44	80.6/91.3
Carbonell (1997) [153]	93	≤63	50 mg/m^2 IM	800 μg[c,d]	3	2 and 2	14	92.5
	98				4			91.8
	96				5			92.7
Wiebe (1999) [154]	45	<49	50 mg/ m^2 IM	600 μg[d]	5 to 7	1 and 7	28	88.9
	55		50 mg/m2 PO	800 μg[d]				94.5
	37		50 mg/m2 IM					97.3
	50		50 mg/m2 PO					90.0
Creinin (1999) [155]	126	≤49	50 mg/ m^2 IM	800 μg[d]	5 to 6	7	14/42	87.3/95.2
	122			800 μg			14/42	81.1/91.8
Carbonell Esteve (1999) [156]	148	≤56	25 mg PO	800 μg[c,d]	7	2 and 2	14	91.2
	154		50 mg PO					90.3
Borgatta (2001) [157]	1987	≤49	50 mg/ m^2 IM	800 μg	4 to 6	1 to 2	43	84.1
Wiebe (2002) [96]	518	≤49	50 mg/ m^2 IM	800 μg[d]	4 to 6	1 and 3	35	94.5

PO = orally
IM = intramuscularly
[a] Self-administered as dry tablets unless otherwise indicated.
[b] Repeated if gestational sac was still present.
[c] Regimen included additional misoprostol 400–1200 μg over a 24-hour period after expulsion confirmed.
[d] Moistened misoprostol.

by misoprostol 800 μg vaginally ($n = 524$) in women up to 49 days' gestation [96]. Women self-administered the misoprostol and repeated the dose 24 hours later if bleeding was less than typical menstrual flow. Subjects returned 7 days after the initiation of treatment for vaginal ultrasonography; those with a persistent gestational sac received misoprostol 800 μg vaginally. A vacuum aspiration was performed if a viable gestation persisted at a second follow-up visit 2 weeks after initiation of treatment or if the gestational sac had not expelled by 5 weeks after initiation of treatment. The abortion rate by the 1-week follow-up examination was 75% in the methotrexate group and 90% in the mifepristone group ($p < 0.001$). Aspiration rates were 4% in both groups. Side effects were similar between the mifepristone/misoprostol and methotrexate/misoprostol regimens with statistically significant differences in the incidence of headache after the mifepristone or methotrexate (19.1% vs. 11.3%, $p = 0.001$), diarrhea after the misoprostol (15.9% vs. 27.0%, respectively, $p < 0.001$), fever after the misoprostol (11.5% vs. 21.7%, respectively, $p < 0.001$), chills after the misoprostol (23.2% vs. 49.3%, respectively, $p < 0.001$), and headache after the misoprostol (28.6% vs. 17.0%, respectively, $p < 0.001$). The mean number of bleeding days was slightly greater with the mifepristone regimen (14.6 vs. 13.3 days, $p = 0.032$), whereas the mean pain score using an 11-point scale was significantly greater with the methotrexate regimen (6.3 vs. 5.8, $p = 0.003$). Overall, this study shows a similar overall efficacy for the two regimens in women up to 49 days' gestation; however, women who use the methotrexate regimen are more likely to expel the pregnancy beyond the first week of treatment.

Misoprostol-alone regimens

Where mifepristone is not accessible, various misoprostol-only regimens are being used. Brazil is the only country that has granted regulatory approval for a medical abortion regimen using only misoprostol. However, its widespread use in countries with restricted abortion laws appears to be associated with reduction in maternal morbidity and mortality [29,30].

Reported regimens differ with respect to several factors, including the intervals between doses (3 to 48 hours), the time point for assessing the outcome (a few days to several weeks), and the gestational age (Table 9.3). These multiple variables make it difficult to determine the most effective regimen. When misoprostol is used alone, the oral route is less effective than the vaginal route [97]. Vaginal doses of 800-μg misoprostol are usually repeated several times at intervals from 3 to 48 hours if abortion has not occurred. Typical success rates range from 85 to 95%, with continuing pregnancies occurring in about 4 to 10% of women. A recent review concluded that the evidence supported a recommendation of using misoprostol 800 μg vaginally every 6, 12, or 24 hours for a maximum of three doses [28].

Although the interval for vaginal administration, ranging in studies from 3 to 24 hours, may not be critical, a recent

Table 9.3 Selected studies with misoprostol 800 μg vaginally without mifepristone or methotrexate for medical abortion.

Primary Author	Number	Gestation (weeks)	Moistened with Saline	# Doses	Interval	Observation Time (days)	Complete Abortion (%)	Continuing Pregnancy (%)
Carbonell (1999) [99]	720	5–9	Yes	3[a]	24h	21	89	6.5
Jain (1999) [158]	100	≤8	Yes	2	24h	1	73	12.0
						15	88	8.0
Ngai (2000) [159]	40	≤9	Yes	3	48h	42	85	2.5
	40	≤9	No	3	48h	42	65	10.0
Bugalho (2000) [160]	103	≤6	Yes	2	7d	1	72	NR
						8	92	NR
Jain (2001) [161]	100	≤8	Yes	3	24h	3	93	5.0
Jain (2002) [102]	125	≤8	Yes	3	24h	1	72	NR
						15	88	4.8
Zikopoulos (2002) [162]	80	≤6	Yes	3[a]	24h	3	96	1.3
	80	6–8	Yes	3[a]	24h	3	86	2.5
Carbonell (2003) [163]	452	5–9	Yes	3[a]	8h	21	91	4.2
Singh (2003) [164]	150	8	Yes	3[b]	3h	43	96	4.0
Von Hertzen (2007) [98]	513	≤9	Yes	3	3h	14	85	3.9
	512	≤9	Yes	3	12h	14	83	4.9

[a] Subjects treated with additional misoprostol once expulsion confirmed.
[b] Repeat doses were 400 μg.
NR = Not reported.
Continuing pregnancy = Viable pregnancy.

WHO trial showed that the interval did matter for sublingual administration, with 3 hours being more effective than 12 hours [98]. Investigators recorded complete abortion rates after 2 weeks of follow-up for 431 (84%) women in the sublingual group and 434 (85%) women in the vaginal group when misoprostol 800 μg was given at 3-hour intervals. However, complete abortion occurred in 399 (78%) and 425 (83%), respectively, when the dosing occurred at 12-hour intervals. The rate of continuing pregnancy also was significantly higher for the 12-hour interval as compared with the 3-hour interval when using sublingual misoprostol (difference 4% [95% CI 0.4, 6.8%], $p = 0.03$) but not for vaginal dosing (difference 1% [95% CI 1.5, 3.5%], $p = 0.44$). The sublingual route was associated with more frequent gastrointestinal side effects (such as nausea, vomiting, shivering, and hyperthermia) than vaginal administration. In this large study, the efficacy was noted to decrease with advancing gestation regardless of route of misoprostol. The risk of failure was twice as high for women at 8 to 9 weeks' gestation compared with those at 7 weeks' gestation or less. This finding is similar to previous studies using misoprostol-only regimens [99].

Misoprostol as a single agent has been used for higher gestational ages, with two studies reporting success rates of 84% to 89% using repeated vaginal doses of 800 μg for women with pregnancies from 9 to 13 weeks' gestation [100,101].

Comparison to mifepristone regimens

A single randomized trial has compared mifepristone and misoprostol to misoprostol alone [102]. This double-blind trial included women up to 56 days' gestation using mifepristone 200 mg ($n = 119$) or placebo ($n = 125$) followed 48 hours later by misoprostol 800 μg vaginally. Misoprostol was repeated every 24 hours up to three doses. Complete abortion rates were 95.7 and 88.0%, respectively ($p < 0.05$). The women who received mifepristone aborted much more quickly and required fewer doses of misoprostol compared to women who received misoprostol alone. Complete abortion by 24 hours after misoprostol treatment was 89.9 and 72.0%, respectively ($p < 0.001$). Women experienced slightly more side effects with the mifepristone regimen, which may be due to a higher rate of treatment success resulting in effects related to the abortion process.

Medical abortion practice

Patient eligibility

Although medical contraindications to abortion with mifepristone, methotrexate, or misoprostol alone are few, social or psychological considerations are more common. Women are not optimal candidates for medical abortion if they:

- wish to minimize participation in their abortion;
- are anxious to have the abortion over quickly;
- cannot return for follow-up visits; or
- cannot communicate easily with the provider because of language or comprehension barriers (phone interactions are more common with medical than with surgical abortion patients).

Due to the risk of teratogenicity in an ongoing pregnancy, women also must intend to have a surgical abortion should the medical method fail. Other nonmedical considerations include access to a telephone in case of an emergency and distance from emergency medical treatment (e.g., suction curettage for hemorrhage). A few reports have examined use of medical abortion by adolescents, with outcomes similar to older women [103,104].

Some medical issues are important regardless of the regimen being used. Most studies exclude anemic women with hemoglobin levels less than 9.5 or 10 g/dl; accordingly, the safety of medical abortion in anemic women is unknown. Transfusion rates with medical abortion are 0.1 to 0.4% in large trials [15,40,63,88,105,106]. Although these rates are low, they exceed that reported for surgical abortion in early pregnancy (0.01%) [107]. Women with a coagulopathy or actively using anticoagulants are excluded from medical abortion studies for similar reasons. Accordingly, providing a medical abortion for a woman with hemoglobin less than 9.5 g/dl or who is anticoagulated warrants caution.

Similarly, medical abortion side effects, although limited in nature, could be consequential in women with severe hyperemesis gravidarum or other conditions that cause nausea, vomiting, or diarrhea. Gynecologic contraindications include suspected ectopic pregnancy and an intrauterine device (IUD) *in situ* that will not be removed. The outcomes for multiple pregnancies do not appear to differ from those for singletons [108].

Misoprostol, the agent commonly used with all regimens, has no contraindications in principle. However, because a small number of female smokers over the age of 35 years experienced adverse cardiac events following sulprostone administration [15], the medical commission in France extended the same restriction to women using misoprostol or gemeprost. In the USA, clinical practice guidelines of the American College of Obstetricians and Gynecologists and the National Abortion Federation do not advise against misoprostol use in smokers [109,110]. In breastfeeding women, small amounts of misoprostol or its active metabolite may appear in breast milk [111]. Thus, breastfeeding or pumping milk for feeding should be avoided for at least 6 hours after misoprostol administration. Breastfeeding women who use methotrexate-misoprostol regimens should pump and discard the milk for 72 hours.

Contraindications to the use of mifepristone or methotrexate regimens include known allergy to any of the agents being used. Because of the antiglucocorticoid properties of mifepristone, women with chronic renal insufficiency and long-term corticosteroid use should not

use mifepristone. Contraindications to the methotrexate regimens include active liver or renal disease. Asthma is not a contraindication for any regimen; both methotrexate and misoprostol are bronchodilators, and mifepristone has no effect on the respiratory system. However, severely asthmatic patients may require chronic corticosteroid therapy, and providers should ask about such medication use prior to administering mifepristone.

Patient education, informed consent, and preparation

As with all abortion methods, the informed consent process must assure that a woman is certain about her decision to have an abortion and that she understands the alternatives available and their risks and benefits (Chapter 5). Patient uncertainty warrants a delay, even if waiting means that she will be unable to choose an early medical option.

The process of medical abortion is quite similar regardless of the agent used, although the timing and efficacy may vary. Patient education (Table 9.4) [112] includes explaining the medical abortion process and ways in which it differs from surgical abortion (Chapter 10). Heavier bleeding and more severe cramping may occur as compared to surgical abortion; describing the bleeding and cramping as comparable to a miscarriage, rather than menses, helps to prepare some patients. Mean days of bleeding are higher with medical (14 days) than surgical abortion (9 days), but days of spotting (about 10) are similar [113]. Increasing gestational age predicts more bleeding or spotting days after medical, but not surgical, abortion.

In contrast to surgical abortion, patients experience passage of the products of conception firsthand, and women may wonder if they will identify the tissue. The pregnancy and the decidua may pass at the same time or separately. The decidualized endometrium commonly appears thick and solid as it passes either in fragments or as a complete decidual cast. The gestational sac and placenta frequently pass intact, often with adherent clot (Figure 9.3). The clots may be quite large and obscure the pregnancy tissue. However, some patients may see a tiny sac or conceptus, particularly if the pregnancy is more than 7 weeks' gestation. Using true-to-size illustrations that show early products of conception may help prepare the patient for this event.

Although complications occur infrequently, providers must provide patients with clear instructions for accessing emergency services in case of hemorrhage. Medical abortion patients with severe hemorrhage or ongoing viable pregnancies warrant uterine aspiration. Therefore, clinicians who are

Table 9.4 Patient education for early medical abortion.

1. Discuss the decision to have an abortion and confirm that it is certain and voluntary.
2. Discuss the treatment alternatives (medical abortion or aspiration) and the benefits and risks of each method.
3. Describe the medical regimens available and their approval status. For mifepristone-misoprostol abortion in the USA, explain the differences between the FDA-approved regimen and other evidence-based regimens. For methotrexate-misoprostol abortion, explain that the FDA has approved these drugs for other uses, but not for medical abortion.
4. Explain what to expect. Bleeding and cramping typically intensify during expulsion of the pregnancy (usually 2–4 hours) and then gradually subside. Passage of clots is common during expulsion; lighter bleeding or spotting typically lasts about 2 weeks, but may be longer.
5. Explain that the patient is unlikely to see products of conception unless she is beyond 7 to 8 weeks' gestation, in which case the embryo will be very small and often obscured by blood clots.
6. Discuss known side effects of the medical abortion regimen including mild gastrointestinal symptoms; short-term fever, warmth, or chills; or oral ulcers (methotrexate only).
7. Explain that the drugs used for medical abortion may increase the risk of birth defects in continuing pregnancies. Emphasize that aspiration is advised if the medical abortion fails.
8. Discuss possible complications including failed abortion, incomplete abortion, hemorrhage, or infection. Emphasize that atypical infections have occurred rarely after use of mifepristone combined with misoprostol (see text).
9. Provide how to insert the misoprostol vaginally (deep into the vagina after washing hands), buccally (tucked between cheek and gum), or sublingually (under the tongue) and how to use pain medications.
10. Explain the time commitment and expected number of visits.
11. Provide 24-hour emergency contact information and emphasize warning signs that may warrant evaluation, including:
    a. Prolonged or heavy bleeding ($\geq$ two soaked maxi pads for 2 consecutive hours);
    b. Fever ($\geq$ 38°C) lasting more than 4 hours or beginning in the days after misoprostol administration;
    c. Abdominal pain or discomfort or "feeling sick" (including weakness, nausea, vomiting, or diarrhea, with or without fever) more than 24 hours after using misoprostol.
12. Provide information about available contraceptive methods and when to initiate the chosen method, if any.
13. Address issues of confidentiality.
14. Review all required consent forms, which must be signed before administration of the medications.

Adapted with permission from Paul M, Stewart F. Abortion. In *Contraceptive Technology* 2008. [112]

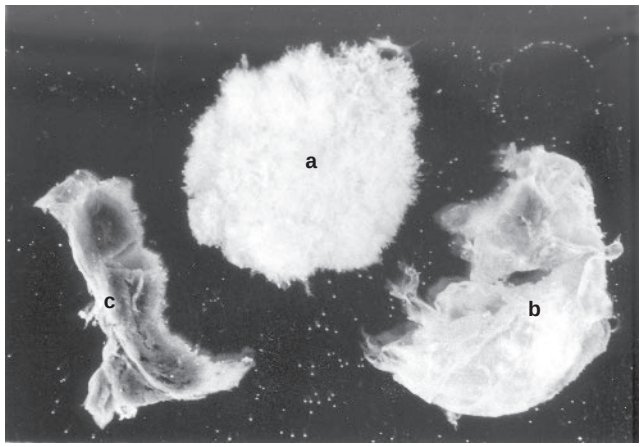

Figure 9.3 Tissue passed within several hours of taking misoprostol (mifepristone abortion). The gestational sac (a) and placenta measure about 3.0 cm. The decidual cast (b) and the blood clot (c) are approximately the same size. (Photographer Daniel Benevento, with permission).

not trained in suction curettage must have collaborative arrangements or referral mechanisms in place for patients who require this intervention.

Treatment

Mifepristone is manufactured in 200-mg tablets and use of doses exceeding 200 mg are of no benefit. In the USA, mifepristone is not available through pharmacies; rather, it is sold by the drug distributor directly to licensed physicians after they sign and return a Prescriber's Agreement. Prescribers agree to report adverse events and to give each patient a Medication Guide to read and a Patient Agreement to read and sign. Instructions for enrolling as a mifepristone provider are available at the distributor's website (http://www.earlyoptionpill.com). Because the distributor's forms pertain to the standard regimen, clinicians who offer an alternative regimen should have patients sign an additional consent or addendum that provides information about the alternative and its benefits and risks.

Due to the impressive accumulation of research on medical abortion, numerous regimens have emerged that are evidence-based, safe, and effective (Table 9.5). The regimen chosen will depend on the availability of medications, cost, patient preference, and other factors. When available, mifepristone regimens offer distinct advantages over other regimens in terms of efficacy, efficiency, and/or side effects.

Women can safely self-administer misoprostol at home. Regardless of route of administration, the same tablets are used as approved for oral dosing. Special suppositories of misoprostol described in some studies are not commercially available and are not necessary. Producing these suppositories and requiring an office visit for misoprostol administration increase cost and inconvenience. When dispensing the tablets, review with the patient how to place the tablets correctly in the vagina, under the tongue, or between the cheek and gums (Table 9.4). With vaginal use, patients need not remain at rest after misoprostol administration or use a tampon to hold the tablets in place.

When using methotrexate, women who are taking folate-containing medications (e.g., prenatal vitamins) should discontinue them for 1 week following methotrexate administration. Some clinicians also advise patients to avoid foods rich in folate, but no studies have evaluated the necessity of this practice.

All unsensitized Rh(D)-negative patients should receive anti-D immune globulin [109,110]. A dose of 50 μg suffices for gestations of 12 weeks or less. If the Rh status is unknown when mifepristone or methotrexate is administered, the patient can receive anti-D immune globulin anytime before or within 72 hours after she uses the misoprostol.

Patients are given appropriate instructions and prescribed oral narcotic analgesics to use if ibuprofen or acetaminophen provides inadequate pain relief. Providers may choose to use narcotics without acetaminophen (e.g., codeine, 30-mg tablets) to allow patients to self-medicate without concern for acetaminophen overdose. Nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen are not contraindicated and do not decrease the likelihood of successful medical abortion after misoprostol administration [114].

Although heavy bleeding is common, the patient needs to know how much bleeding is considered too much. Typical instructions include advising the patient to contact the provider if she soaks two sanitary pads per hour for 2 hours in a row. Clinicians who receive such calls can talk to the woman at 20-minute to 30-minute intervals until the bleeding slows, as long as the patient is feeling all right. Advise the patient to seek emergency care if the bleeding does not slow down; the urgency depends on how the patient is feeling, her baseline hemoglobin, and how far she is from emergency treatment.

Follow-up typically occurs 2 weeks after initiation of treatment if the provider is using clinical evaluation to determine outcome; it can be scheduled sooner if vaginal ultrasonography is used. Sonography should be used only as a means of determining the presence or absence of the gestational sac (Figure 9.4) and not for measurement of endometrial thickness when deciding if a medical abortion is successful. Most protocols with mifepristone or methotrexate include follow-up approximately 1 week after initiating treatment, whereas protocols using misoprostol alone follow women at frequent intervals to assess the need for repeat dosing. If the gestational sac remains, women have the option of a repeat dose of misoprostol (administered in the office or self-administered at home), expectant management (if the pregnancy is nonviable), or a vacuum aspiration should she want to complete the abortion without further delay. Approximately 20 to 30% of women using mifepristone or

Table 9.5 Comparison of medical abortion regimens.

	Standard Mifepristone-Regimen	Alternative Mifepristone- Misoprostol Misoprostol Regimens	Methotrexate-Misoprostol Regimens	Misoprostol-Only Regimens
Gestational Age Limit	49 days	63 days; efficacy continues throughout first trimester, but studies have included in-hospital observation	49 days	63 days
Mifepristone Dose	600 mg oral[a]	200 mg oral	N/A	N/A
Methotrexate Dose	N/A	N/A	50 mg/m^2 IM or 25–50 mg oral[b]	N/A
Misoprostol Dose	400 μg oral; administered during second office visit	800 μg vaginal, buccal, or sublingual; tablets supplied during first office visit and administered at home	800 μg vaginal; tablets supplied during first office visit and administered at home	800 μg vaginal; other routes can be used but are not well studied, have more side effects, or are not as effective
Misoprostol Timing	36–48 hours after mifepristone	24 hours after mifepristone for all routes; vaginal misoprostol may be used earlier, with studies supporting simultaneous administration of misoprostol and mifepristone up to 63 days' gestation	3–7 days after methotrexate	Every 6, 12, or 24 hours for a maximum of three doses
Advantages and Drawbacks	Some women prefer the oral route of misoprostol administration	Compared to regimens using oral misoprostol: extends gestational age eligibility, higher complete abortion rates, fewer side effects, more flexibility in timing of misoprostol	Useful in areas with limited access to mifepristone	Useful in areas with limited access to mifepristone, but not as effective as mifepristone-misoprostol regimens

[a] Mifepristone 200 mg oral followed by misoprostol 400 μg oral 36–48 hours later is also effective up to 49 days' gestation.

[b] Methotrexate tablets come in 2.5-mg doses, so packaging the tablets into gelatin capsules facilitates administration.

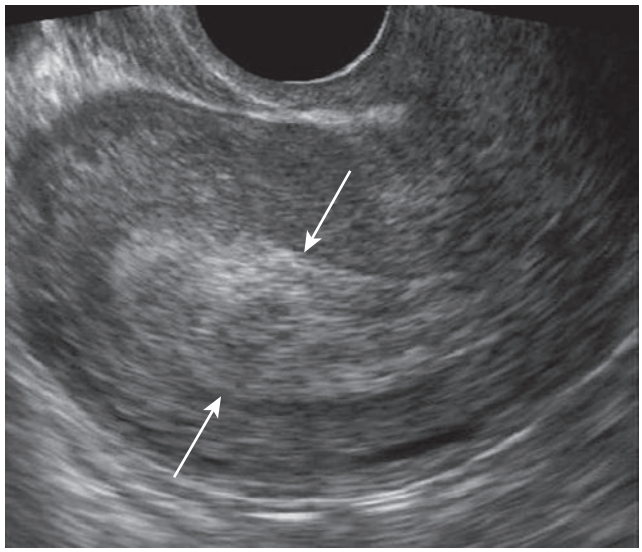

Figure 9.4 Vaginal ultrasound examination of uterine cavity 1 day after medical abortion. Heterogeneous intracavitary echoes are present (arrows) but no gestational sac is visible. These findings are consistent with successful abortion and do not require intervention.

methotrexate regimens will abort following a second dose of misoprostol [40,88,115,116]. Follow-up is scheduled for 1 week, although some methotrexate studies have delayed this second follow-up for 4 weeks if gestational cardiac activity is absent.

A few studies have attempted to investigate alternative methods of follow-up, including human chorionic gonadotropin (hCG) evaluation. Serum hCG is predictive of expulsion when values obtained before and 24 hours after misoprostol treatment are compared [117]. The average decline with successful treatment is 66% with a lower limit of 50% considered acceptable. Monitoring hCG values 1 week after treatment also can be used, with a decline of 80% indicating success [118,119]. Urine hCG testing 1 or 2 weeks after treatment is not clinically useful whether high or low sensitivity tests are used [120] (Chapter 6). An evaluation of nearly 1,000 women suggests that clinical history alone is as or more predictive than any of these objective measures [121].

Methotrexate regimens include the possibility that women who do not abort following misoprostol treatment will expel the pregnancy after a delay of a few days to a few weeks. On average, this event will happen approximately 3 to 3½ weeks after methotrexate administration. While waiting for the pregnancy to pass, the patient's bleeding and pregnancy symptoms will subside. Usually, she will have slight cramping or light bleeding a day or two before expulsion occurs. Of the women who have to wait for the pregnancy to pass, approximately 96% will abort completely within 35 days after the methotrexate injection [115]. Whereas mifepristone and misoprostol-only regimens commonly include a vacuum aspiration if expulsion has not occurred within 2 weeks, women with a nonviable pregnancy could be treated in the same way (expectant management) should they not desire surgical intervention.

Because medical abortion is not 100% effective, patients need access to surgical abortion services if the medical method fails or if significant hemorrhage occurs. Clinicians who offer medical abortion but not aspiration abortion must ensure the availability of 24-hour back-up coverage that includes competent surgical abortion services.

Side effects and complications

Bleeding

The mean duration of bleeding is 9 days, but the range is from 1 to 45 days; some women bleed until their next menstrual period. The average drop in hemoglobin is 0.7% [62]. The few women who present with excessive bleeding typically do so at least 10 days after misoprostol, and most have retained pregnancy tissue. Vacuum aspiration, which is rarely emergent, can be performed at this point.

Abdominal pain and cramping

The majority of women experience some cramping; for most women, it is like an intense menstrual period. Pain medication use varies significantly between countries. Narcotic pain medicine is used by 60% of women in the UK [20]. In a French study, when women were asked to rate their pain on a visual analog scale on the day of misoprostol use, the mean rating was 3.1 (0 = no pain at all, 10 = unbearable pain) [62]. Clinicians commonly advise women to use an NSAID or other non-narcotic pain medication initially and to add a narcotic medication if needed. Because the dose of acetaminophen must not exceed 4 grams in a 24-hour period to avoid liver toxicity, use of narcotics without acetaminophen (e.g., codeine or oxycodone) allows women to use as much as they need to ensure adequate pain control.

Gastrointestinal distress

Many women experience some nausea, vomiting, or diarrhea. However, these symptoms are generally self-limiting and usually resolve 2 to 6 hours after taking misoprostol. Diarrhea appears to be less frequent with vaginal administration of misoprostol and more common when women are exposed to higher serum levels of misoprostol, as with sublingual administration.

Infection

Endometritis is a rare complication of medical abortion, which typically involves no instrumentation of the cervix or uterine cavity. In large trials including 1,000 participants or more, infection rates typically vary from 0.1 to 0.9% [15,40,63,87,91,122]. A review of medical abortion studies suggests that the infection rate is approximately 0.9% [123].

Severe neutropenia has been described in two women who received methotrexate 50 mg/m^2 intramuscularly for the treatment of ectopic pregnancy [124]. A sustained fever exceeding 38°C following the use of methotrexate, especially if stomatitis is also present, requires a complete blood count for evaluation of neutropenia. In the very rare event of severe neutropenia following the use of methotrexate, the theoretical risk of secondary opportunistic infection warrants appropriate preventive measures.

Whereas some clinicians recommend the universal use of perioperative antibiotics for surgical abortion [125], no data currently exist to support such treatment with medical abortion. Rare fatal infections with *Clostridium sordellii* and *perfringens* have been reported in North America in women who received mifepristone and misoprostol [126,127]. Symptoms seen with such infections include weakness, nausea, vomiting, or diarrhea with or without abdominal pain that persists after expulsion of the pregnancy. Although patients typically lack a fever, they exhibit rapid pulse, low blood pressure, and very high red and white blood cell counts. The US Centers for Disease Control and Prevention have also reported deaths from the same organism after other reproductive outcomes (Chapter 15), including in two women who had spontaneous abortions without use of mifepristone or misoprostol [128]. On the basis of available information, serious infection and death from medical abortion seem most likely related to the physiologic process of abortion, whether spontaneous or induced, and not the medicines themselves.

Teratogenicity

The risk of congenital anomalies in pregnancies that continue after administration of medical abortifacients is a concern. Methotrexate is an antimetabolite that can damage a fetus; however, most reports of teratogenicity involve high doses used for chemotherapy or doses exceeding normal ranges [129,130]. A review of teratogenicity with low-dose oral methotrexate in early pregnancy found no effect [130]. No reports have linked any teratogenic effects to mifepristone.

Misoprostol, however, has been associated with multiple congenital anomalies whether used alone or with other agents, albeit the risk is low. Case reports suggesting its potential teratogenicity were first reported in 1991 from Brazil, where abortion is highly restricted and misoprostol was commonly used to induce abortion illegally [131]. Malformations most likely are due to disruption of the blood supply to the developing embryo during misoprostol-induced myometrial contractions. Central nervous system and limb defects are the most commonly reported anomalies, specifically Möbius syndrome, which is characterized by congenital facial paralysis with or without limb defects. A recent meta-analysis including 4,899 cases of congenital anomalies and 5,742 controls showed an increased risk for any congenital defect (OR = 3.56 [95% CI 0.98, 12.98]), Möbius sequence (OR = 25.31 [95% CI 11.11, 57.66]) and terminal transverse limb defects (OR = 11.86 [95% CI 4.86, 28.90]) [132].

Uterine rupture

Another concern about the use of medical abortion regimens using a prostaglandin analog is the risk of uterine rupture, especially in women with previous uterine scarring. Case reports of uterine rupture are rare in first-trimester medical abortion [133,134]. Four case series of women with prior uterine surgery (primarily cesarean sections) have been reported. These series include women who received mifepristone and oral misoprostol [135,136] and methotrexate and vaginal misoprostol [137] for medical abortion, and women who received vaginal misoprostol alone for treatment of early pregnancy failure [138]. They include a total of 392 women with no reported uterine rupture, giving a 95% confidence interval of 0 to 0.8%.

Acceptability

Early medical abortion is well accepted. Acceptability appears to be driven primarily by efficacy (i.e., when women are asked if a regimen is acceptable, they will view one with high efficacy positively) [139]. To no surprise, all studies that ask women if the experience was positive report a high percentage of favorable responses regardless of the regimen, typically with more than 80% of women finding the method acceptable [140–143].

Few studies have evaluated factors that affect acceptability. Findings are similar for all types of medical abortion regimens. Women who have had a prior surgical abortion are somewhat less likely to choose a medical method for a future abortion as compared to women who have never experienced a surgical abortion [142–144].

Although studies indicate that women prefer oral administration of misoprostol, this type of inquiry is questionable because it presumes that all else is equal (e.g., efficacy, side effects, risks). Accordingly, Lohr et al [89] attempted to evaluate factors beyond overall acceptability by asking women about their feelings regarding buccal administration of misoprostol. As expected, most women who used the mifepristone and buccal misoprostol regimen would choose the method again (91%), and almost all (97%) would recommend the option to a friend. With further open-ended questioning, however, 72% disliked the buccal route; only 6% said so because the regimen did not work. Forty-three per cent of women found the taste of buccal administration objectionable; 30% found buccal retention uncomfortable; and 10% experienced oral irritation, numbness, or oral ulcers.

Henshaw and colleagues [145] followed women who chose their method of abortion and those with no preference who were then randomized to the standard regimen

of mifepristone and misoprostol or vacuum aspiration under general anesthesia. Although 95% of women who elected medical abortion would choose it again, only 74% of those randomized to medical abortion would choose that option again. A similar disparity was evident for women who had a surgical abortion; 90% of those who chose, and 87% of those who were randomized and received, a surgical abortion would choose that option again. The lower acceptability for women who were randomized to medical abortion only applied to those more than 49 days' gestation. This study suggests that women with no preference tend to be happy with either method early in pregnancy.

Interestingly, Creinin [146] randomized 50 women up to 49 days' gestation to medical or surgical abortion. The medical abortion regimen included methotrexate 50 mg/m^2 intramuscularly followed 5 to 6 days later by misoprostol 800 μg self-administered vaginally at home. The surgical abortion method involved manual vacuum aspiration with local anesthesia in the office. Of the women randomized to aspiration, 92% stated they would choose a surgical procedure for a next abortion, whereas only 63% of women randomized to a medical abortion would choose that option in the future ($p < 0.001$).

Conclusion

Mifepristone in combination with misoprostol or another prostaglandin analog is the most effective and efficient abortifacient combination. Acceptable gestational age limits for using mifepristone depend on the type and route of administration of the prostaglandin analog. Regimens using mifepristone with gemeprost are effective through 63 days' gestation. When mifepristone is combined with oral misoprostol 400 μg, complete abortion occurs in more than 90% of women through 49 days' gestation. Using misoprostol 800 μg vaginally results in high efficacy through 63 days' gestation or more. Although less studied, buccal or sublingual misoprostol administration appears to have similar efficacy to vaginal regimens, albeit with more side effects. Unlike vaginal administration, regimens with buccal misoprostol may not be effective with time intervals of less than 24 hours.

In some countries where mifepristone is not available, methotrexate and misoprostol can be effective for abortion up to 49 days'gestation when methotrexate is administered as either 50 mg/m^2 intramuscularly or 50 mg orally. As with mifepristone regimens, efficacy is highest under 42 days' gestation and appears to decrease after 49 days, but no sharp decline is evident at any particular gestational age. The overall efficacy of methotrexate regimens is achieved only with patience, as only about 60% to 75% of women expel the pregnancy during the week after misoprostol treatment.

The more commonly used alternative when mifepristone is not accessible is misoprostol alone. The recommended regimen up to 63 days' gestation is 800 μg vaginally every 3 to 24 hours for a maximum of three doses. As an alternative, sublingual misoprostol shows similar efficacy to the vaginal route when 800 μg is given at 3-hour, but not 12-hour, intervals. Side effects appear to occur more frequently following sublingual administration. When available, mifepristone regimens are preferable. Whereas the continuing pregnancy rate after mifepristone followed by a single vaginal dose of 800 μg misoprostol is less than 1% (Table 9.1) in pregnancies up to 9 weeks' gestation, it rises to 4 to 10% with misoprostol-alone regimens using vaginal or sublingual dosing (Table 9.3). Complete abortion rates are also about 10 to 15% higher with combination regimens.

Overall, medical abortion is effective, safe, and acceptable to women. Because most women find a regimen acceptable if it works, studies have begun to examine acceptability of misoprostol dosing methods in more depth. These studies suggest that buccal or sublingual dosing produces side effects that may make the regimens less acceptable than vaginal dosing. More research into what factors women feel are important other than efficacy will help us to provide the best medical abortion options for each patient.

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