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The Mifepristone-Misoprostol Regimen for Early Medical Abortion

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The combination of mifepristone, an antiprogesterone known in the United States as Mifeprex (Danco Laboratories, New York, NY), and misoprostol, a prostaglandin analogue marketed in the United States under the brand name Cytotec (Pharmacia [formerly Searle], Peapack, NJ), provides a nonsurgical abortion in the early stages of a pregnancy. Mifepristone blocks the action of progesterone, a hormone necessary to sustain a pregnancy, whereas misoprostol causes contractions that expel the embryo and other pregnancy tissue. Since September 2000, mifepristone has been approved by the United States Food and Drug Administration for induced abortions of gestations of 49 days or less since the last menstrual period, but is not yet approved for any other uses. Misoprostol has long been approved to prevent and treat stomach ulcers.

Introduction

Extensive worldwide experience during more than a decade demonstrates the safety, effectiveness, and acceptability of the mifepristone-misoprostol regimen, both to care providers and patients. Regulatory agencies in more than 20 countries (Table 1) have approved this early option regimen, which has now been used by millions of women. In the United States, the Food and Drug Administration's (FDA) approval in September 2000 followed a lengthy application process. Since then, mifepristone has become available in 45 US states and the District of Columbia, and major health insurers have added coverage for mifepristone for eligible women (Data from Danco Laboratories). In addition, clinical studies with various mifepristone-misoprostol regimens have indicated that the method can be used safely and effectively in both developed and developing countries, including China, Cuba, India, Tunisia, and Vietnam.

Even before medical abortion methods were approved in the United States, researchers began testing variations

of the original French mifepristone-misoprostol regimen to simplify its provision and make it more convenient and accessible. These variations include lowering the mifepristone dosage, allowing women to self-administer the misoprostol at home, administering the misoprostol vaginally instead of orally, and making the timing of mifepristone administration more flexible [1•].

This article provides an overview of mifepristone-misoprostol medical abortion. This includes the way it is provided under the traditional, FDA-approved regimen; studies that suggest alternative regimens and procedures; acceptability of the treatment; and future directions.

Food and Drug Administration-approved Standard Regimen

The FDA-approved regimen is similar in many respects to the one originated and still used in France (and elsewhere). The Population Council's submission for FDA approval was based largely on the French pivotal studies, and the clinical trial conducted in 17 US clinics with 2121 women followed the French regimen [2].

Almost all women can use mifepristone-misoprostol medical abortion. Table 2 lists contraindications to these drugs [3].

Under the currently approved regimen, treatment with oral mifepristone and oral misoprostol requires three office visits for most women [4]. After counseling and a physical exam, an eligible woman takes one oral dose of three 200-mg tablets of mifepristone (600 mg total). Two days later, the woman returns to the clinic for misoprostol. If the woman's pregnancy has not ended with use of mifepristone alone (mifepristone is successful by itself in 2% to 5% of cases), she takes two 200- μ g tablets of misoprostol orally (400 μ g total). She then receives instructions about possible side effects and about whom to contact for questions and emergencies [3]. Approximately 12 days later, she returns to the clinic to confirm that the abortion is complete, or to have the process completed if it is not [3,5•].

At the follow-up visit or sooner, a complete abortion can be confirmed clinically or through ultrasonography. If an ongoing pregnancy with cardiac activity is confirmed through ultrasonographic examination, a vacuum abortion should be performed [2,3].

Table 1. Countries where mifepristone has been approved for early medical abortion

Year	Country
1988	France, China
1991	United Kingdom
1992	Sweden
1999	Austria, Belgium, Denmark, Finland, Germany, Greece, Israel, Luxembourg, the Netherlands, Spain, Switzerland
2000	Norway, Russia, Ukraine, United States
2001	Tunisia, South Africa

Data from the Population Council, August 2001.

Table 2. Contraindications to mifepristone and misoprostol*

Mifepristone
Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass
Intrauterine device in place
Chronic adrenal failure
Current long-term systemic corticosteroid therapy
History of allergy to mifepristone
Hemorrhagic disorders or concurrent anticoagulant therapy
Inherited porphyria
Misoprostol
Allergy to misoprostol or other prostaglandins
Uncontrolled seizure disorder
Acute inflammatory bowel disease

*There are no data on the safety and efficacy of mifepristone in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory, or renal disease; insulin-dependent diabetes mellitus; severe anemia; or heavy smoking.
Data from Food and Drug Administration [3,4].

Table 3. Side effects of mifepristone-misoprostol early medical abortion

Side effects of mifepristone use appear to be similar to symptoms many women experience during normal pregnancy; side effects following oral misoprostol use are more severe and more closely resemble a heavy period or even an early miscarriage:
Cramps and abdominal pain similar to those associated with a menstrual period or a natural miscarriage
Uterine bleeding, heavier than a heavy period and lasting at least 1 week, or bleeding and spotting that is not heavy but that can last for 1–3 weeks (in rare cases, if uterine bleeding is extremely heavy or prolonged, the patient may require curettage and/or blood transfusion)
Nausea and vomiting, sometimes requiring medication
Diarrhea (very rare)

Data from Spitz et al. [2].

Data from three large French and American trials showed complete abortion rates at less than 49 days of gestation ranging from 92% to 97% percent [5]. From 2% to 5% of the patients typically will require vacuum aspiration to resolve an incomplete abortion, end a continuing pregnancy, or control bleeding [1•].

Clinicians familiar with medical abortion describe it as being indistinguishable from a spontaneous miscarriage in terms of cramping and bleeding [5•]. Also, as with spontaneous abortion, a woman's experiences with early medical abortion tend to be quite variable. Some women have complete expulsion of the embryo within a few hours of misoprostol administration, whereas others take longer; some women have relatively little discomfort, whereas others have pain and nausea [5•]. Typical experiential side effects of this treatment, however, are described in Table 3.

In clinical trials in the United States, 84% of the women aborted within 24 hours of taking misoprostol [2]. Patients usually are aware when the products of the pregnancy are passed, but until close to 9 weeks of gestation, they will generally see only blood and possibly placental tissue that they might perceive as clots [5•]. Vaginal bleeding is not evidence of termination of pregnancy, but lack of bleeding usually indicates failure [3]. Bleeding, usually heavier than a normal menses, can last for a median of 9 to 13 days. The heaviest bleeding (when the expulsion occurs) can last for 1 to 4 hours, but may vary; it tends to taper off quickly [5•]. Rarely, women have continued to bleed or spot for as many as 2 months after a complete abortion. Heavy bleeding requiring a blood transfusion is the most serious potential side effect; in the US clinical trial, one woman per 1000 required a transfusion [2]. Although continued bleeding

might seem worrisome to both patients and clinicians inexperienced with medical abortion, a comparative study with surgical abortion showed that clinical indicators, such as significant drops in hemoglobin, are no different [6].

Under current FDA labeling, mifepristone can be administered only in a clinic or medical office, by or under the supervision of a physician who can assess the gestational age of an embryo, diagnose ectopic pregnancies, and assure patients' access to emergency medical facilities [3,4]. As part of extensive required counseling, the provider must make sure before giving the medication that the patient understands the procedure and is prepared to have a surgical abortion should the medical abortion fail [3,4]. The FDA requires patients to review information about the treatment in a medication guide and to sign a patient agreement [3]. If the physician does not perform surgical abortions, referral arrangements with a physician experienced in performing abortions must be made in advance [3]. Although these restrictions limit to a certain extent the kind of physician who can provide mifepristone, they are generally not considered too onerous (basically, any physician who can handle a miscarriage can provide a medical abortion). Such physicians include obstetricians/gynecologists, family practitioners, pediatricians, and internists [5•].

Mifepristone (Mifeprex; Danco Laboratories, New York, NY) is distributed in the United States by Danco Laboratories, L.L.C. It is not available by prescription at pharmacies [4,5•], but rather is distributed directly to providers.

Evidence-based Regimens

Even before mifepristone was approved in the United States for early medical abortion, various clinical trials were exploring alternative regimens and doses. Results suggest the variations may be as, or more, effective and convenient than the FDA-approved regimen [1•,5•]. (FDA guidelines state that an approved product may be used for a purpose not included in its labeling if there is published evidence to support such use [7].)

Variations studied to date include lower doses of mifepristone (200 mg total instead of 600 mg); vaginal insertion of 800 µg of misoprostol (double the oral dose); at-home self-administration of misoprostol, either orally or vaginally; adjusting the timing of treatment with vaginal misoprostol; and extending the gestational age for the regimens to 56 or even 63 days (or beyond) [5•]. Researchers have also explored whether ultrasonography was necessary to confirm gestational age and abortion outcome [5•]. Although these variations are not yet FDA-approved, many providers in the United States already use them routinely based on current evidence. Planned Parenthood Federation of America, for

instance, permits its providers to use 200 mg of mifepristone followed by home use of misoprostol (Planned Parenthood Federation of America, unpublished data).

Lower mifepristone dose

A mifepristone dose lower than 600 mg should work, researchers say, because mifepristone is rapidly but variably absorbed after oral administration [8]. Peak serum levels are similar after mifepristone doses ranging from 100 mg to 800 mg [8]. The World Health Organization (WHO) first raised the possibility of providing less than a 600-mg dose of mifepristone as early as 1991. Results from a WHO randomized trial reported in 1993 demonstrated that doses of 200 mg of mifepristone were just as effective as doses of 400 mg and 600 mg [9]. In that WHO trial, however, mifepristone was followed after 48 hours with vaginal administration of gemeprost, a prostaglandin E1 analogue slightly different from the prostaglandin (misoprostol) currently approved in the United States. Complete abortion rates for women less than or equal to 56 days of gestation were nearly identical in all three dosage groups, ranging from 93.8% to 94.3%, with overall continuing pregnancy rates of 0.4% [9].

Several large studies since then have also reported effective results using a lower dose of mifepristone and using misoprostol instead of gemeprost, but direct comparison of the regimens with the FDA-approved standard is difficult because the route of misoprostol administration in those latter studies was vaginal instead of oral. A retrospective analysis of 2000 women who were given 200 mg of mifepristone followed 36 to 48 hours later by 800 µg of misoprostol vaginally showed an overall success rate of 97.5%, with a success rate of 98.5% for women whose pregnancies were less than 49 days [10]. In this same group, 3.2% aborted after taking only mifepristone, similar to the rate reported with women who had taken 600 mg of the drug [2]. Continuing pregnancy in women with 49 or fewer days of gestation was 0.2%, lower than the 0.8% to 1.5% reported in studies with 600 mg mifepristone followed by orally administered misoprostol [2]. Even among 1072 women with gestation from 50 to 63 days, only 0.8% aborted before taking misoprostol, but 96.7% had complete abortions after vaginal misoprostol administration, a rate higher than that reported with the standard regimen [2,10]. Incomplete abortion was reported at 3.2%, whereas 0.8% of the women had ongoing pregnancies [2,10].

In another trial conducted in the United States, similar results for 933 women whose gestations were less than 56 days were reported after doses of 200 mg of mifepristone and 800 µg of misoprostol administered vaginally [11,12•]. The success rate in that trial was 97%, with only a 0.3% rate of ongoing pregnancy [11,12•].

Oral misoprostol beyond 49 days of gestation

The 1994 Population Council clinical trial, on which FDA approval was partially based, tested the traditional regimen up to 63 days of gestation with 600 mg of mifepristone and 400 µg of oral misoprostol [2]. The abortion success rates appeared to decline with increasing gestational age: the success rate for women of 49 days of gestation or less was 92%, but the rate declined to 83% percent for women up to 56 days of gestation, and to 77% for women up to 63 days of gestation [2].

Why did the success rates drop so much at the later gestations? Clinicians who participated in this trial later told researchers that because the trial extended the allowable gestational age beyond the standard French protocol of 49 days, they were more anxious about women in days 50 to 63 and were, therefore, quicker to intervene if they had any doubts [13]. More experienced providers of mifepristone medical abortion are more relaxed with the method and intervene less often, leading to higher chances of success.

The link between provider experience and success is also evident in data from French studies that extended the gestation age beyond 49 days. With treatment of 600 mg of mifepristone and 400 µg of oral misoprostol, more than 93% of 380 women from 50 to 56 days of gestation had successful abortions, as did 86.8% of 235 women from 57 to 63 days of gestation [14].

Vaginal administration of misoprostol

Vaginal administration of misoprostol may work better than oral mifepristone in later gestations of between 50 and 63 days, although the research is not yet clear. Two studies [10,12•] investigated effectiveness in women up to 56 days of gestation using 600 mg of mifepristone and 800 µg of misoprostol vaginally. Results of the smaller study (166 women) showed the treatment was 96% effective, whereas the larger study (933 women) had a complete abortion rate of 97%. The continuing pregnancy rate of 1.1% was higher among women from 50 to 56 days of gestation, but only two of 660 women less than 49 days had continuing pregnancies [10,12•].

A randomized trial with patients up to gestational age of 63 days tested treatments in which all 233 women were given 600 mg of mifepristone, but approximately half were administered 800 µg of oral misoprostol and half had 800 µg of vaginal misoprostol [5•,15]. Overall, 95% of the women who were given vaginal misoprostol had complete abortions—most within 4 hours—compared with the 87% of the patients who were given oral misoprostol. Further analysis showed, however, that the success differences were concentrated in the women with gestational ages over 49 days. Taken as a whole, the vaginal misoprostol group had fewer ongoing pregnancies (1% compared with 7% in the oral misoprostol users), whereas the incidence of incomplete abortion was similar. Interestingly, in that study, the incidences of vomiting and diarrhea were significantly lower in the women whose misoprostol was administered vaginally [15].

Timing of misoprostol administration

The standard regimen calls for administration of misoprostol 2 days after mifepristone use. Based on the fact that mifepristone has a half-life of approximately 30 hours [8], however, a recent US study [16•] sought to determine whether vaginal misoprostol could actually be administered any time during 1, 2, or 3 days after mifepristone. A total of 2295 women less than or equal to 56 days of gestation was randomly assigned to self-administer 800 µg of vaginal misoprostol at home 1, 2, or 3 days after taking 200 mg of mifepristone. Results showed complete medical abortion rates of 98% among those taking their misoprostol 1 day after mifepristone, 98% among those using the standard interval of 2 days, and 96% for those waiting 3 days in administering their misoprostol [16•]. The researchers concluded that there is no medical reason to wait 48 hours for vaginal misoprostol administration [16•].

In-home self-administration of misoprostol

Numerous studies of the mifepristone-misoprostol regimen demonstrate the safety and effectiveness of self-administration of misoprostol at home [5•]. Home use is also very acceptable to American women [5•]. Two studies of 1000 American women of 56 days or less of gestation who self-administered vaginal misoprostol at home showed a success rate of 97%. When given the choice of taking misoprostol in the physician's office or at home, 98% of the women opted for in-home self-administration. In a study with 933 women, 94% found the procedure acceptable. No significant complications were reported with at-home use of misoprostol, and side effects were similar to those reported for women who used misoprostol in the clinic [11,12•].

Home use is also safe, effective, and acceptable in resource-poor settings, including those with little sophisticated back-up infrastructure. In Tunisia and Vietnam [17], the FDA-approved regimen was simplified to reduce the mifepristone dose to 200 mg and to permit home use of the misoprostol. Among the 315 women of less than or equal to 56 days of gestation who were offered the option of taking 400 µg misoprostol orally at home or in the clinic, roughly 88% chose home administration. When asked about their choice, many women mentioned convenience: taking the drug at home was more compatible with their domestic or work duties, or they were more comfortable at home. Women returned to the clinics for follow-up 2 weeks after taking mifepristone, and those with incomplete medical abortions received surgical abortions. Complete abortion rates averaged 93% in Vietnam and 91% in Tunisia, very similar to the literature for clinic administration of the standard French regimen. Overall, approximately 90% of women were very satisfied or somewhat satisfied with the simplified medical abortion regimen [17].

Because of the inconsistency of dose and route of administration of mifepristone and misoprostol in the studies conducted during the past few years, the Population Council, the

Table 4. Best- and least-liked features of mifepristone-misoprostol early medical abortion

Best-liked features
Avoidance of surgery or anesthesia
Perceived "naturalness" of the procedure
Privacy and control; compatibility with other duties and obligations
Least-liked features
Long period of bleeding
Pain
Uncertainty about whether the method would work or had worked
Large number of clinic visits, particularly in some clinical trials
Data from Winikoff et al. [20].

US sponsor of mifepristone, is conducting a study with a reduced mifepristone dose of 200 mg combined with an oral misoprostol dose of 400 µg. The study also permits home administration of misoprostol to document safety and acceptability. If the study finds that the lower dose of mifepristone followed by misoprostol taken at home is safe and effective, the data will be submitted to the FDA to petition for an appropriate change in the official label. With these changes, the approved mifepristone-misoprostol regimen could become simpler to use, more private, and less expensive.

Ultrasonography

Nearly all medical abortion research in the United States has used ultrasound, but this has not been true in other countries. Research from places where they have been tried finds that bimanual examination and women's estimates of their last menstrual period are fairly accurate. In France and Vietnam, for example, primarily only clinical dating parameters have been used with good results [18]. Ultrasound may be helpful to confirm a diagnosis to determine if a pregnancy is ectopic before starting treatment or in cases where the clinician suspects an ongoing pregnancy [after] mifepristone-misoprostol use [5•].

In fact, women themselves can often manage to estimate the gestational ages of their pregnancies. A recent study in Pune, India and Atlanta, GA, assessed whether women seeking early abortions could accurately calculate pregnancy duration. The 422 women used a simple worksheet and calendar to calculate the duration of gestation based on the date of their last menstrual period and/or unprotected intercourse [19]. Clinicians who used standard clinic practices (including ultrasound in nearly all the cases in Atlanta) to estimate pregnancy duration then examined the women. Most of the women (97% in Atlanta and 96% in Pune) could produce some estimate of pregnancy duration and most of these (85% in Atlanta and 93% in Pune) were within 2 weeks of the estimates made by providers. The study concluded that most women [in that study] who sought early abortion could accurately calculate pregnancy duration within a margin of error clinically inconsequential for unsafe use of unsupervised medical abortion [19].

Acceptability

Clinical studies of the mifepristone-misoprostol regimen generally ask women to comment on the experience. Most of the responses have been favorable. Ninety-six percent of the women who participated in the Population Council US clinical trial said they would recommend the regimen to another woman seeking an abortion, and more than 90% said they would choose the method again if they needed another abortion [20]. In every case in which it has been studied, acceptability of medical abortion is very high among women who have used it [5•,20–23]. Women who experienced in-home, self-administered misoprostol also expressed high levels of satisfaction with the method [10,12•,16•]. Table 4 summarizes the best- and least-liked features of mifepristone-misoprostol abortion.

Future

Availability of mifepristone for early medical abortion could enhance women's choices in the United States by increasing the number of providers who offer abortions. A survey of health professionals who do not currently offer abortion services indicated growing interest in providing medical abortion among family practice physicians, obstetricians/gynecologists, nurse practitioners, and physician's assistants [24]. Whereas slightly more than half of family practice physicians said they were not at all likely to provide medical abortion, 31% said they were very likely or somewhat likely. Forty-five percent of obstetricians/gynecologists were very likely or somewhat likely to prescribe mifepristone. The surveys also shed light on providers' concerns that mifepristone abortions might take too much time or have too many procedural requirements. These concerns might be allayed by changes in the traditional regimen, including home use of misoprostol, which should reduce the number of office visits.

It is possible that the new Population Council clinical trial currently underway will result in labeling changes that will permit lower doses of mifepristone and at-home self-administration of oral misoprostol. Lower mifepristone doses could lower the cost of medical abortion. Because

Table 5. Resources for information on medical abortion

<p>The Center for Reproductive Health Research and Policy Stewart FH, Wells ES, Flinn SK, Weitz TA: <i>Early Medical Abortion: Issues for Practice</i>. UCSF Center for Reproductive Health Research and Policy: San Francisco CA. 2001. (For copies, write to: Felicia Stewart, University of California San Francisco, Center for Reproductive Health Research and Policy, 3333 California Street, Suite 335, San Francisco, CA 94143-0744)</p> <p>American College of Obstetricians and Gynecologists American College of Obstetricians and Gynecologists, Committee on Practice Bulletins. Medical Management of Abortion. <i>ACOG Practice Bulletin, Number 26, April 2001</i>. American College of Obstetricians and Gynecologists: Washington DC. 2001 (For copies, write to: The American College of Obstetricians and Gynecologists, 409 12th Street, SW, PO Box 96920, Washington DC 20090-6920. (ISSN 1099-3630)</p> <p><i>American Journal of Obstetrics and Gynecology (supplement)</i> Paul M, Creinin MD, eds. Early medical abortion. <i>American Journal of Obstetrics and Gynecology</i> 2000, 183(suppl2). Contains 11 original articles on medical abortion topics, ranging from history of the regimens to legal issues, to management of side effects and complications, to counseling.</p> <p><i>Journal of the American Medical Women's Association (supplement)</i> <i>Journal of the American Medical Women's Association</i> 2000, 55(suppl3). Nearly two dozen submissions, typically from leading international experts, cover the various regimens, the social context of medical abortion, and provider and patient perspectives. The supplement also addresses the international experience with medical abortion, both in developed and developing countries.</p> <p>http://www.earlyoptions.org The National Abortion Federation runs this website, full of practical information, including their national toll-free hotline that can help women locate a medical abortion provider near them. A concise history of mifepristone appears on the site, as does information about other methods of medical abortion, such as methotrexate.</p> <p>http://www.earlyoptionpill.com Danco, the distributor of Mifeprex (mifepristone) runs this webpage. It contains the FDA-approved patient information sheet, prescribing information, order forms for obtaining supplies of mifepristone and other useful information for both patients and providers.</p>

misoprostol was originally approved for oral use, however, an attempt by the misoprostol (Cytotec) manufacturer (Pharmacia [formerly Searle], Peapack, NJ) to change the labeling to include vaginal use is unlikely to happen.

Postmarketing activities requested by the FDA include a study of patient outcomes in cases where physicians refer their patients needing surgical intervention, compared with patient outcomes when physicians perform surgical procedures themselves, and establishment of a system for surveillance, reporting, and tracking rare ongoing pregnancies after treatment with mifepristone. Data from these studies too could help to refine and adapt the mifepristone-misoprostol regimen of early medical abortion to needs in the United States.

Conclusions

A wealth of clinical research, published data, and practical experience support the provision of mifepristone and misoprostol for early medical abortion. Expanded use of the drug combination in Europe, in the developing world, and in the United States should further bolster confidence in the regimen's safety, efficacy, and acceptability. A list of resources regarding medical abortion can be found in Table 5.

Disclaimer

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for-profit research organization that receives royalties from the marketer of Mifeprex. The authors have no personal financial interest in mifepristone or any other regimen of early medical abortion. This article represents the personal views of the authors.

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