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SOUNDING BOARD

Sixteen Years of Overregulation: Time to Unburden Mifeprex

Mifeprex REMS Study Group

On March 29, 2016, the Food and Drug Administration (FDA) approved an updated label for Mifeprex (mifepristone 200-mg tablets, Danco Laboratories), the product that is commonly used in the United States in combination with misoprostol to induce a medical abortion. The changes made to the label were sweeping: they included a more effective dosing regimen containing less mifepristone and more misoprostol, expansion of the gestational limit for treatment from 49 to 70 days, omission of the recommendation for in-person follow-up, removal of language indicating that the prescriber must be a physician, and elimination of the requirement to report nonfatal adverse events. These revisions were supported by extensive data about mifepristone that have been accumulated since the FDA first approved the drug in 2000.[1-7] Professional guidelines for medical abortion had already incorporated many of the new procedures,[8-10] and thus the FDA's action brought the drug label into line with current standard practice.

The new label will undoubtedly have substantial benefits. Because the label now conforms with scientific evidence, it will reduce confusion among women, providers, and policymakers about the appropriate use of the drug. Moreover, it is expected to make abortion less expensive, more convenient, and more widely available in the handful of states where legislatures have enacted laws requiring adherence to the FDA-approved Mifeprex label.[11]

We suggest, however, that in merely updating the label, the FDA did not go far enough: the distribution of Mifeprex remains substantially and unnecessarily encumbered by a Risk Evaluation and Mitigation Strategy (REMS), which was left fundamentally unchanged.

A REMS is a set of restrictions beyond the label that the FDA may impose under the authority of the federal Food, Drug, and Cosmetic Act (FDCA) when necessary to ensure that the benefits of a drug outweigh its risks.[12,13] REMS programs are intended for drugs that are known or suspected to cause serious adverse effects that cannot be mitigated simply by the label instructions. The FDCA includes six factors that the FDA should consider when deciding whether to require a REMS, including the benefits and risks of the drug, the duration of treatment, the number of expected users, and the background risk of adverse events in the population (see Box). Each REMS is customized to address the specific risks of a given drug. The REMS for clozapine, which is indicated for the treatment of schizophrenia, is illustrative: because the drug can cause severe neutropenia, its REMS requires, among other measures, that pharmacists verify that each patient has had a recent neutrophil count before dispensing the drug.[14] At this time, 74[12] of the approximately 1750 prescription drug and therapeutic biologic active ingredients that have been approved by FDA and marketed in the United States[15] have REMS programs.

The core of the Mifeprex REMS is three provisions designated as "elements to assure safe use."[16] First, the drug may be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber; it may not be sold in retail pharmacies. Second, to prescribe the drug, a health care provider must become "certified" by completing and sending a form to the drug distributor attesting that he or she can assess pregnancy duration, diagnose ectopic pregnancy, and provide surgical intervention if needed, either personally or by referral. Third, each woman taking Mifeprex must be given an FDA-approved medication guide and sign an FDA-approved patient agreement that summarizes the use instructions specified in the label and the potential risks of the drug. Whereas drug labels are generally not binding for individual clinicians[17] — misoprostol, for example, is approved for the prevention of gastric ulcers but is legally and widely used off-label for gynecologic purposes,

Excerpts from the Food, Drug, and Cosmetic Act Relevant to Risk Evaluation and Mitigation Strategies.*

a. Submission of proposed strategy

1. Initial approval

If the Secretary . . . determines that a risk evaluation and mitigation strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug, and informs the person who submits such application of such determination, then such person shall submit to the Secretary as part of such application a proposed risk evaluation and mitigation strategy. In making such a determination, the Secretary shall consider the following factors:

A. The estimated size of the population likely to use the drug involved.
B. The seriousness of the disease or condition that is to be treated with the drug.
C. The expected benefit of the drug with respect to such disease or condition.
D. The expected or actual duration of treatment with the drug.
E. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
F. Whether the drug is a new molecular entity.
G. Assuring access and minimizing burden.

. . .

f. Providing safe access for patients to drugs with known serious risks that would otherwise be unavailable

1. Allowing safe access to drugs with known serious risks

The Secretary . . . may require that the risk evaluation and mitigation strategy for a drug include such elements as are necessary to assure safe use of the drug, because of its inherent toxicity or potential harmfulness, if the Secretary determines that —

A. the drug, which has been shown to be effective, but is associated with a serious adverse drug experience, can be approved only if, or would be withdrawn unless, such elements are required as part of such strategy to mitigate a specific serious risk listed in the labeling of the drug; and
B. for a drug initially approved without elements to assure safe use, other elements . . . are not sufficient to mitigate such serious risk.

2. Assuring access and minimizing burden

Such elements to assure safe use . . . shall:

A. be commensurate with the specific serious risk listed in the labeling of the drug;
B. within 30 days of the date on which any element . . . is imposed, be posted publicly by the Secretary [of Health] with an explanation of how such elements will mitigate the observed safety risk;
C. considering such risk, not be unduly burdensome on patient access to the drug, considering in particular —

i. patients with serious or life-threatening diseases or conditions; and
ii. patients who have difficulty accessing health care (such as patients in rural or medically underserved areas); and

D. to the extent practicable, so as to minimize the burden on the health care delivery system —

i. conform with elements to assure safe use for other drugs with similar, serious risks; and
ii. be designed to be compatible with established distribution, procurement, and dispensing systems for drugs.

* Information is quoted from the Food Drug and Cosmetic Act, Section 505-1, codified at 21 U.S.C. §355-1.

such as labor induction[18] — compliance with a REMS is mandatory and consequently has a nationwide effect.

When Mifeprex was first approved 16 years ago, documented experience with its use outside a research context was minimal, and the restrictions to minimize potential harm were perhaps understandable. Since then, however, its effectiveness and safety have been definitively established. To date, 19 deaths have been reported to the FDA among the more than 3 million women in the United States who have used Mifeprex (Long A, Danco Laboratories: personal communication); the estimated Mifeprex-associated mortality rate is thus 0.00063%. In contrast, the background risk of pregnancy-related death among pregnant women in the United States who do not have abortions and instead proceed to live birth is approximately 0.009%, which is 14 times higher.[19] Studies that together included more than 423,000 women around the world who had a medical abortion have reported that the rates of nonfatal serious adverse events after mifepristone use, such as hospital admission, blood transfusion, or serious infection, range from 0.01 to 0.7%, and these events are almost always treatable without permanent sequelae.

Side effects such as bleeding, cramping, fever, and chills are typically minor and transient.[2] This reassuring safety record and the fact that each woman using Mifeprex receives only a single pill, which virtually eliminates the potential for substantial misuse, suggests that Mifeprex no longer fits the expected profile of a drug that requires a REMS.

Indeed, in our view, the Mifeprex REMS is inconsistent with the express requirements of the FDCA. The law states that a REMS may include the elements to assure safe use only if the "inherent toxicity or potential harmfulness" of the drug is such that no other means are available to mitigate a "specific serious risk" listed on the label. If included, the elements must be "commensurate" with this risk and must include an explanation of how the elements will mitigate this risk. In addition, the elements must not unduly burden either patient access to the drug — especially among patients with serious medical conditions and patients in medically underserved areas — or the health care system (see Box).

The Mifeprex elements do not meet these specifications. Mifepristone is not inherently toxic or harmful to the woman using it. The notion that the elements are essential to ensure that its benefits outweigh its risks has no basis in evidence; on the contrary, other countries that have not instituted regulations similar to the REMS have not encountered substantial safety problems. One or both of the two serious risks described on the Mifeprex label — atypical infection and prolonged heavy vaginal bleeding — also may occur after many other common obstetrical and gynecologic procedures, including vaginal delivery, medical and surgical management of miscarriage, and insertion of intrauterine devices. All these procedures are routinely performed without federally mandated provider certification, signed patient agreements, or venue limitations, and yet they are generally considered to be acceptably safe. In this context, a rationale for singling out Mifeprex as needing such measures to ensure safety is lacking, and the Mifeprex elements can hardly be justified as "commensurate" with the risks.

Similarly in conflict with the law, the Mifeprex REMS provides no explanation as to how the elements to assure safe use — in particular, the restriction on dispensing sites — could possibly have any effect on the risks of infection or bleeding. The new Mifeprex label permits a woman to take the drug after leaving the dispensing facility, and the pharmacologic effects do not begin for hours after ingestion. If a serious complication were to occur, the location where the woman had obtained the tablets would be entirely irrelevant to her clinical outcome. In fact, recent research has shown that allowing each woman who has a medical abortion to take the mifepristone in the place of her choosing is safe and is preferred by many women.[20-22]

The Mifeprex elements to assure safe use plainly impede women's access to the drug.[11] For example, the prohibition on sale at retail pharmacies and the provider certification requirement mean that a qualified clinician who has not completed the certification process and arranged to stock the drug in his or her office cannot provide timely medical abortion care to a woman who presents unexpectedly. Consequently, treatment of such a patient would be delayed, increasing cost and inconvenience and, if the delay is substantial, possibly even medical risk. The elements also complicate the provision of medical abortion through telemedicine,[23] which has proved valuable in improving access in rural areas.[24] More generally, the expense and hassle of maintaining drug inventories as well as reluctance to be included on a list of certified abortion providers — understandable, given the long history of harassment and violence[25] — may discourage some otherwise willing clinicians from offering medical abortion at all. Considering the severe shortage of abortion providers in many parts of the United States and the long distances that many women must travel to obtain abortion services,[26] we contend that any barrier to access that has no demonstrated benefit is excessive.

Finally, the Mifeprex elements to assure safe use violate the statutory requirement to minimize the burden on the health care delivery system. In particular, the elements are not compatible with established drug-distribution systems; instead, the Mifeprex distributor has had to set up an onerous and costly infrastructure, used only for this one drug, to enable clinicians to submit certification forms and order supplies. This process certainly does not conform to the distribution system for other drugs with similar serious risks. Anticoagulants can cause major bleeding at numerous anatomic sites, including the vagina,[27-29] and phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction are estimated to be associated with death in up to 0.004% of users,[30] and yet

these drugs do not have REMS programs. Antibiotics, antihypertensive agents, and insulin also can induce immediate serious or fatal reactions shortly after use, but most of these also are not restricted by REMS. In addition, the Mifeprex elements may impede the development of potentially cheaper, generic mifepristone products for abortion by requiring any generic developer either to negotiate a shared distribution system with the distributor of Mifeprex or to set up a separate, parallel system.

Given the data and experience that have been accumulated since the initial FDA approval, the Mifeprex REMS no longer makes clinical sense. The provider certification criteria can technically be met by any health care professional with the ability to read an ultrasound report and familiarity with emergency services, and thus the certification process itself — which is a self-certification without any validation component — is, in essence, an empty formality. Serious complications of mifepristone treatment are uncommon and are very familiar to clinicians who provide care to women of reproductive age; these risks should be manageable through routine labeling and standard clinical counseling. And abortion providers certainly can evaluate patients and prescribe mifepristone without having tablets physically present in their offices.

Medical abortion is a key component of women's health care because it enables effective, safe, private pregnancy termination when surgical abortion is unavailable, clinically contraindicated, or personally undesirable. Mifepristone is currently the only drug approved for medical abortion in the United States, and more than a third of women who present for abortion within the first 8 weeks of gestation now choose to use it. Some evidence suggests that access to this drug can reduce the demand for induced abortion in the second trimester.[31] The Mifeprex REMS impedes the provision of Mifeprex without offering any demonstrated or even reasonably likely advantage. We recommend that the REMS be expeditiously withdrawn.

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The authors, who are members of the Mifeprex REMS Study Group, are Elizabeth G. Raymond, M.D., M.P.H., Kelly Blanchard, M.Sc., Paul D. Blumenthal, M.D., M.P.H., Kelly Cleland, M.P.H., Angel M. Foster, D.Phil., M.D., Marji Gold, M.D., Daniel Grossman, M.D., Mary K. Pendergast, J.D., Carolyn L. Westhoff, M.D., and Beverly Winikoff, M.D., M.P.H. From Gynuity Health Projects (E.G.R., B.W.) and Columbia University (C.L.W.), New York, and Albert Einstein College of Medicine, Bronx (M.G.) — all in New York; Ibis Reproductive Health, Cambridge, MA (K.B.); the Division of Family Planning Services and Research, Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford (P.D.B.), and Advancing New Standards in Reproductive Health, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, San Francisco (D.G.) — both in California; the Office of Population Research, Princeton University, Princeton, NJ (K.C.); the Faculty of Health Sciences, University of Ottawa, Ottawa (A.M.F.); and Pendergast Consulting, Washington DC (M.K.P.).

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VIEWPOINT

HEALTH CARE REFORM

Increasing Access to Abortion With Telemedicine

Elizabeth G. Raymond, MD, MPH
Gynuity Health Projects, New York, New York.

Erica Chong, MPH
Gynuity Health Projects, New York, New York.

Paul Hyland, MBBS
Tabbot Foundation, Sydney, Australia.

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For many women in the United States, obtaining an abortion is unduly difficult. In 2008, a national survey found that 31% of patients in rural areas traveled more than 100 miles for abortion services.[1] Subsequently, states have enacted hundreds of new restrictions on abortion, including limits on the construction of facilities, the qualifications for clinicians, and the procedures that are used for abortion.[2] At present, Mississippi, Missouri, South Dakota, and North Dakota each have only 1 operational outpatient abortion clinic, and Wyoming has none. Once a woman reaches an abortion facility, she may encounter additional barriers, including verbal harassment by protestors and physical blocking of the clinic entry.[3] This harassment is sometimes violent: in November 2015, 3 people were killed at a Planned Parenthood clinic in Colorado Springs, Colorado. The health consequences of impeding access to abortion may be serious: women may delay the procedure, which increases risk, or resort to unsafe abortion methods. Ultimately, some women may be unable to obtain an abortion at all, resulting in unwanted births.

Assuring women's access to legal abortion is essential. One emerging approach leverages telemedicine to obviate the need for a patient to visit an abortion clinic. Although surgical abortion requires an in-person visit with a physician or advance practice clinician, medical abortion, which in 2011 accounted for 23% of abortions in the United States,[4] is an ideal fit for telemedicine. Medical abortion with mifepristone and misoprostol has few contraindications within the first 10 weeks of gestation (Box),[5] all of which can be assessed using interview, laboratory testing, and ultrasonography; physical examination is not routinely required. The abortifacient medications are self-administered. The abortion itself occurs at home. Treatment outcome is evaluated 1 to 2 weeks later by ultrasonography or by serum or urine human chorionic gonadotropin (HCG) tests; increasingly, this follow-up occurs remotely. The efficacy and safety of early medical abortion is high: surgical uterine evacuation is needed for less than 5% of patients, and major complications, such as hemorrhage or infection requiring hospitalization, occur in less than 0.4%.[6]

In 2008, a Planned Parenthood affiliate in Iowa initiated the first formal telemedicine abortion program in the United States. The program is designed to enable provision of medical abortion at collaborating clinics that stock the abortifacient drugs but that do not have physicians on site. To use this program, a woman has screening laboratory tests and an ultrasound performed at one of these clinics, which sends the results to a physician in another location. After reviewing the results and speaking with the patient by videoconference, the physician authorizes the clinic to dispense the abortifacient medications if appropriate. In its first year of operation, this program nearly tripled the number of sites in Iowa offering abortion services, from 6 to 17. Among 233 women with follow-up, the treatment was fully effective in 98.7%. One patient had a blood transfusion in an emergency department; no other serious adverse events were reported. The telemedicine service was rated highly by both patients and clinicians.[7]

An alternate telemedicine model uses a direct-to-patient approach, in which the abortifacient drugs are provided directly to eligible patients by mail or by prescription. The advantage of this approach is that the patient is not required to visit a clinic that has mifepristone in stock; instead, she obtains the screening tests locally, and she can speak with the clinician from her home. This feature enhances privacy and autonomy as well as access. The dispersion of care also helps to avoid harassment of both patients and clinicians.

Direct-to-patient telemedicine is being used in settings outside the United States. One program that mails mifepristone and misoprostol to women in countries without access to safe abortion services has treated about 50 000 women in about 90 countries since 2006 and by 2014 was receiving 2000 queries a month from women requesting help with medical abortions.[8,9] In 2012, a direct-to-patient telemedicine service was instituted in British Columbia, Canada.[10] That service to date has used methotrexate instead of mifepristone because the latter medication was not approved in Canada until July 2015. As of December 2015, the program had provided medical abortions to 33 women with no serious complications (E. Wiebe, MD; email communication; December 22, 2015).

In September 2015, a direct-to-patient telemedicine abortion service was launched in Australia. The program, which one of us (P.H.) founded and directs, serves women in 5 Australian states and territories that include 90% of the population. This program uses a standard regimen of mifepristone and misoprostol, screens each patient with an interview, blood tests, and ultrasonography, and confirms abortion success using serum and urine HCG testing. As of mid-December 2015, the program had served 303 women, of whom 41% were from Tasmania, an island state with restricted access to abortion. About 90% completed a planned 10-day follow-up contact, a higher proportion than is typical after in-person medical abortion in the United States. Only 6 women required a face-to-face clinical encounter after treatment, and no serious complications have been reported. Nearly all patients rated the service very highly.

Direct-to-patient telemedicine abortion is unavailable in the United States. The primary reason is that the Risk Evaluation and Mitigation Strategy (REMS) for mife-

Corresponding Author: Elizabeth G. Raymond, MD, MPH, Gynuity Health Projects, 15 E 26th St, Ste 801, New York, NY 10010 (eraymond@gynuity.org).

pristone established by the US Food and Drug Administration (FDA) mandates that mifepristone be dispensed to patients in clinics, medical offices, and hospitals. The drug is not available in pharmacies, so it cannot be prescribed, and a common interpretation of the REMS is that it prohibits mailing the medication as well. These restrictions are medically unjustified: mifepristone, which is dispensed in single doses, has no immediate clinical effects, and thus the location where a patient receives it, or even where she swallows it, is irrelevant to its efficacy or safety. Notably, the prescribing limitations impede not only telemedicine but also in-person provision of medical abortion by clinicians who do not maintain inventories of mifepristone in their offices.

Broad expansion of telemedicine for abortion in the United States is further restricted by medical practice rules in a number of states. Some states require an in-person examination before a clinician may issue any prescription via telemedicine unless 1 or more specific exceptions are met. These rules limit prescriptions of mifepristone to women that the clinician has already seen, effectively eliminating any benefit of telemedicine. In addition, some states require that the patient be in the presence of a health care provider during the conversation with the clinician who is at a remote location, which makes direct-to-patient telemedicine impossible. Nineteen states have specifically banned telemedicine abortion, either explicitly or by requiring the clinician and patient to be in the same place (see the eTable in the Supplement).

The challenges and barriers notwithstanding, work is under way to increase access to telemedicine abortion services in the United States. The Iowa model is being expanded to other states where it is legally permitted. Later in 2016, a pilot study of direct-to-patient telemedicine abortion is expected to begin in several settings around the country; because of the mifepristone REMS, this study will be conducted under an Investigational New Drug Application filed with the FDA. Legal challenges to telemedicine abortion bans have been filed in Iowa and Idaho, and in July 2015, the Iowa Supreme Court overturned the ban in that state. Our hope is that such efforts will help to improve access to abortion, especially in circumstances in which obtaining this basic health care is otherwise inconvenient, intimidating, or entirely infeasible.

Box. Contraindications to Medical Abortion With Mifepristone and Misoprostol[a]

- Gestational age exceeding established limit for regimen[b]
- Confirmed or suspected ectopic pregnancy
- Intrauterine device in place
- Chronic adrenal failure
- Concurrent long-term corticosteroid therapy
- History of allergy to mifepristone, misoprostol, or other prostaglandin
- Hemorrhagic disorders or concurrent anticoagulant therapy
- Inherited porphyrias

[a] Adapted from US Food and Drug Administration–approved label for mifepristone.

[b] The regimen most widely used in the United States for outpatient abortions is comprised of mifepristone, 200 mg, followed 24 to 48 hours later by misoprostol, 800 µg taken buccally. Although not all professional guidelines currently are in agreement, the National Abortion Federation recommends that this regimen is safe and effective through 70 days of gestation.

ARTICLE INFORMATION

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Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss

Courtney A. Schreiber, M.D., M.P.H., Mitchell D. Creinin, M.D., Jessica Atrio, M.D., Sarita Sonalkar, M.D., M.P.H., Sarah J. Ratcliffe, Ph.D., and Kurt T. Barnhart, M.D., M.S.C.E.

ABSTRACT

BACKGROUND

Medical management of early pregnancy loss is an alternative to uterine aspiration, but standard medical treatment with misoprostol commonly results in treatment failure. We compared the efficacy and safety of pretreatment with mifepristone followed by treatment with misoprostol with the efficacy and safety of misoprostol use alone for the management of early pregnancy loss.

METHODS

We randomly assigned 300 women who had an anembryonic gestation or in whom embryonic or fetal death was confirmed to receive pretreatment with 200 mg of mifepristone, administered orally, followed by 800 μg of misoprostol, administered vaginally (mifepristone-pretreatment group), or 800 μg of misoprostol alone, administered vaginally (misoprostol-alone group). Participants returned 1 to 4 days after misoprostol use for evaluation, including ultrasound examination, by an investigator who was unaware of the treatment-group assignments. Women in whom the gestational sac was not expelled were offered expectant management, a second dose of misoprostol, or uterine aspiration. We followed all participants for 30 days after randomization. Our primary outcome was gestational sac expulsion with one dose of misoprostol by the first follow-up visit and no additional intervention within 30 days after treatment.

RESULTS

Complete expulsion after one dose of misoprostol occurred in 124 of 148 women (83.8%; 95% confidence interval [CI], 76.8 to 89.3) in the mifepristone-pretreatment group and in 100 of 149 women (67.1%; 95% CI, 59.0 to 74.6) in the misoprostol-alone group (relative risk, 1.25; 95% CI, 1.09 to 1.43). Uterine aspiration was performed less frequently in the mifepristone-pretreatment group than in the misoprostol-alone group (8.8% vs. 23.5%; relative risk, 0.37; 95% CI, 0.21 to 0.68). Bleeding that resulted in blood transfusion occurred in 2.0% of the women in the mifepristone-pretreatment group and in 0.7% of the women in the misoprostol-alone group (P=0.31); pelvic infection was diagnosed in 1.3% of the women in each group.

CONCLUSIONS

Pretreatment with mifepristone followed by treatment with misoprostol resulted in a higher likelihood of successful management of first-trimester pregnancy loss than treatment with misoprostol alone. (Funded by the National Institute of Child Health and Human Development; PreFaiR ClinicalTrials.gov number, NCT02012491.)

From the Pregnancy Early Access Center (PEACE), Division of Family Planning (C.A.S., S.S.), Department of Obstetrics and Gynecology (C.A.S., S.S., K.T.B.), University of Pennsylvania, Philadelphia; the Department of Public Health Sciences, University of Virginia, Charlottesville (S.J.R.); the Department of Obstetrics and Gynecology, University of California, Davis, Sacramento (M.D.C.); and the Department of Obstetrics and Gynecology, Montefiore Hospital and Albert Einstein College of Medicine, Bronx, NY (J.A.). Address reprint requests to Dr. Schreiber at the Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, PA 19104, or at schreibe@upenn.edu.

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A Quick Take is available at NEJM.org

First-trimester miscarriage, or early pregnancy loss, is the most common complication in pregnancy and affects approximately 1 million women in the United States annually.[1,2] Subtypes of early pregnancy loss include anembryonic gestation and embryonic or fetal death, inevitable abortion, and incomplete abortion.[3,4] Before the advent of home pregnancy testing and early ultrasonography, women often presented with heavy bleeding or signs of infection requiring prompt treatment with dilation and curettage.[5] Currently, women frequently receive a diagnosis of early pregnancy loss before the onset of symptoms. This decrease in exigent presentations has led to an interest in pursuing nonsurgical treatment options for pregnancy loss.[6,7] Although some women pursue expectant management, women generally prefer active management[6,8-12]; the ability to have control over the management of miscarriage may relieve some of the emotional burden that accompanies first-trimester pregnancy loss.[12-14]

Medical management of early pregnancy loss with prostaglandin analogues allows for planned, expedited expulsion of the nonviable pregnancy tissue, with the goal of avoiding a surgical procedure. Misoprostol is stable at room temperature and can be administered by the woman herself, which allows the tissue expulsion to occur in the privacy of a woman's home at a time she chooses.[15] Medical management is highly desired by many women, and the use of misoprostol is recommended by society guidelines in the United States and throughout the world.[16,17] Unfortunately, the standard dose of 800 μg of misoprostol, administered vaginally, has low efficacy among women with a closed cervical os. As many as 15 to 40% of such women require a second dose of misoprostol, which prolongs the treatment period, or ultimately require the uterine evacuation procedure they wished to avoid.[3,7-9,18] The rate of failure diminishes the clinical usefulness of this strategy in practice.[12]

Mifepristone is a 19-nor steroid that acts as a competitive progesterone-receptor antagonist and a glucocorticoid-receptor antagonist and primes the myometrium and cervix for prostaglandin activity.[15,19,20] The reported effectiveness of combination treatment with mifepristone and misoprostol for early pregnancy loss has ranged from 52 to 95%.[3,10,11,21,22] This wide range is due in part to heterogeneity in study designs and outcome definitions.[3] To date, the usefulness of mifepristone in the treatment of early pregnancy loss has remained unclear. We performed a randomized trial to compare the efficacy and safety of pretreatment with mifepristone followed by treatment with misoprostol with misoprostol use alone for the management of anembryonic gestation and embryonic or fetal death in women in clinically stable condition who have a closed cervical os.

METHODS

TRIAL DESIGN

From May 2014 through April 2017, women who received a diagnosis of anembryonic gestation or embryonic or fetal death were referred to the study team for screening; an investigator confirmed eligibility before enrollment. All participants provided written informed consent. The Comparative Effectiveness of Pregnancy Failure Management Regimens (PreFaiR) trial was approved by the institutional review boards at the University of Pennsylvania, the University of California, Davis, and the Albert Einstein College of Medicine. All the authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol. Mifepristone (Mifeprex) was purchased from the manufacturer (Danco Laboratories) at a research price for use in the trial and was dispensed at the trial sites; the manufacturer had no other role in the trial. The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.

PARTICIPANTS

Healthy women 18 years of age or older were eligible if they had an ultrasound examination that showed a nonviable intrauterine pregnancy between 5 and 12 completed weeks of gestation. We excluded women who had an incomplete or inevitable abortion (defined as the absence of a gestational sac, an open cervical os, or both) because of the high efficacy of misoprostol use alone in women with these diagnoses.[4] Women were also excluded if they had a contraindication to mifepristone or misoprostol, had any evidence of a viable or ectopic pregnancy, had a hemoglobin level lower than 9.5 g per deciliter, had a

Donna J. Harrison, M.D.
Executive Director
American Association of Pro-Life Obstetricians and Gynecologists
P.O. Box 395
Eau Claire, MI 49111-0395

Quentin L. Van Meter, M.D., FCP
President
American College of Pediatricians
P.O. Box 357190
Gainesville, FL 32635-7190

December 16, 2021

Re: Docket No. FDA-2019-P-1534

Dear Drs. Harrison and Van Meter:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on March 29, 2019, on behalf of the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians (Petition). In the Petition, you request that FDA: (1) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (2) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

Specifically, in your Petition you request that the Agency:

(1) Restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to include the following:

- Indications and Usage - Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days gestation.

- Dosage and Administration:
  - Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

  - The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
w ww.fda.gov

You also cite information in Box 1, Features of Medical and Surgical Abortion (page 3) in the ACOG Practice Bulletin No. 143.[70] As mentioned above, the ACOG Practice Bulletin No. 143 has been withdrawn and the language you cite is not included in the current Practice Bulletin No. 225.

d. Adverse Event Reporting

In the Petition, you assert that even under the regimen approved in 2000, it was difficult to collect accurate and complete adverse event information for Mifeprex, and that collecting such information is virtually impossible under the regimen approved in 2016 because prescribers only are required to report deaths associated with Mifeprex (Petition at 12). You also assert that FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events (Petition at 12). You state that certified prescribers should at a minimum be required to report the following to FDA's MedWatch reporting system and to the sponsor: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications, including detailed information on these events (Petition at 13).

We acknowledge that there is always a possibility with any drug that some adverse events are not being reported, because reporting to the Agency's MedWatch program by health care professionals and patients is voluntary. We do not agree, however, that the 2016 changes to the prescriber reporting requirements limit our ability to adequately monitor the safety of mifepristone for medical termination of pregnancy. Prior to the 2016 approval of the S-20 efficacy supplement, we assessed approximately 15 years of adverse event reports both from the Applicant and through the MedWatch program and determined that certain ongoing additional reporting requirements under the Mifeprex REMS, such as hospitalization and blood transfusions, were not warranted. This assessment was based on the well-characterized safety profile of Mifeprex, with known risks occurring rarely, along with the essentially unchanged safety profile of Mifeprex during this 15-year period of surveillance. Accordingly, the Prescriber Agreement Form was amended as part of our 2016 approval of the S-20 efficacy supplement to require, with respect to adverse event reporting, only that prescribers report any cases of death to the Applicant.

We also note that the reporting changes to the Prescriber Agreement Form as part of our 2016 approval do not change the adverse event reporting requirements for the Applicants. Like all other holders of approved NDAs and ANDAs, the Applicants are required to report all adverse events, including serious adverse events, to FDA in accordance with the requirements set forth in FDA's regulations (see 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81). FDA also routinely reviews the safety information provided by the Applicants in the Annual Reports. As with all drugs, FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

[70] Petition at 11. Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.