



FDA RESTRICTIONS ON MIFEPRISTONE: TIME FOR A CHANGE?

**Recent studies confirm clinical and cost effectiveness for
medical management of early miscarriage**

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Mifepristone, a drug used to manage early miscarriage or end an early pregnancy, carries unique restrictions imposed by the U.S. Food and Drug Administration (FDA). Patients are required to pick up the drug in person from a doctor or a clinic, even though they can take the drug at home. In July, a federal court ruled that the FDA must suspend these restrictions during the COVID-19 pandemic, for patients seeking an early abortion, although the ruling did not apply to women with an early pregnancy loss. But the challenges to FDA restrictions on mifepristone predate the pandemic. This Issue Brief provides the context for this ongoing controversy, and reviews recent evidence on the clinical and cost effectiveness of mifepristone for the medical management of first trimester miscarriage.

INTRODUCTION

The FDA approved mifepristone (also known as RU486) in 2000 with safety restrictions that involve a Risk Evaluation and Mitigation Strategy (REMS). Under REMS, mifepristone must be dispensed through registered clinicians only, and patients must sign an FDA-approved agreement before receiving the medication. By most accounts, these restrictions stem from the use of mifepristone, in combination with another medication, misoprostol, for medically-induced early abortion. As a result, mifepristone is not available through retail or mail-order pharmacies, and most physicians do not stock the drug.

In the 20 years since then, medical professional organizations and advocacy groups have challenged these restrictions in court, citing evidence of drug's safety and efficacy. In July 2020, a federal district court held that the FDA could not enforce these restrictions on women seeking a medical abortion during a pandemic, because of the risk posed by requiring in-person visits to pick up the medication. The ruling raises longer-term questions about whether the FDA should reconsider the REMS restrictions entirely, especially in light of recent evidence on the clinical and cost effectiveness of mifepristone in the medical management of early miscarriage.



MIFEPRISTONE PRETREATMENT AND PREGNANCY LOSS

Each year, more than one million women in the United States miscarry in the first trimester. Often, ultrasound reveals a nonviable pregnancy, and women face the difficult and painful choice of waiting for a miscarriage to progress, or surgical or medical interventions to help complete the miscarriage process. Many women prefer medical management (medications that they can take at home to induce uterine contractions) rather than surgery (uterine aspiration). The most commonly used medical therapy is misoprostol (self-administered), which fails about 30% of the time, leading to prolonged treatment or eventual surgical management. Another option is to give women mifepristone first (orally) followed by misoprostol, 24 hours later. However, the FDA restrictions on mifepristone have limited access to the drug and, until recently, the efficacy of pretreating with mifepristone was unclear in these circumstances.

RANDOMIZED TRIAL SHOWS MIFEPRISTONE PRETREATMENT IS 25% MORE EFFECTIVE THAN MISOPROSTOL ALONE

Courtney Schreiber and colleagues conducted a randomized trial of mifepristone pretreatment in 300 women with early pregnancy loss, and assessed its efficacy and safety compared to misoprostol only. The landmark [study](#), published in the *New England Journal of Medicine*, found that pretreatment with mifepristone was more 25% more effective than misoprostol alone in successful management of early pregnancy loss.¹ The combination of drugs led to completion of the miscarriage after one course of treatment in 83.8% of women, compared to 67.1% of women receiving misoprostol alone. Fewer women in the pretreatment group needed eventual surgical intervention (8.8% vs. 23.5%). In terms of safety, the study found no significant difference between the groups in adverse events (infections or blood transfusions).

The study provided compelling evidence that pretreatment with mifepristone is safe and effective for women with early pregnancy loss. After the study was released in 2018, the [American College of Obstetrics and Gynecology](#) called for the removal of “outdated” REMS requirements for mifepristone, saying that the restrictions substantially limit access to a safe, effective medication.

MIFEPRISTONE PRETREATMENT IS COST EFFECTIVE

Another consideration in the use of mifepristone pretreatment is whether it is cost effective, at roughly \$90 a pill (misoprostol alone can cost less than one dollar). Schreiber and colleagues conducted an

economic evaluation alongside the clinical trial to estimate the cost-effectiveness of adding mifepristone to the medical management of miscarriage. In a [study](#) published in earlier this year in *JAMA Network Open*, they found that mifepristone pretreatment represents good value from both the perspective of the health sector and society.²

They analyzed direct health care costs in the 30 days after enrollment in the trial, as well as more indirect societal costs such as patients’ time and lost wages. They found that average health care costs were the same in the two groups: in 2018 dollars, \$697 for women receiving mifepristone and misoprostol versus \$691 for women receiving misoprostol alone. From the societal perspective, average costs per patient were \$3,846 for mifepristone and misoprostol and \$4,846 for misoprostol alone — a \$1,000 difference.

REMS AND THE REGULATION OF MIFEPRISTONE

Currently, the FDA has 59 REMS programs in place, 86% of which include “elements to assure safe use” such as clinician registration or special training. The programs are usually applied to drugs with serious complications or contraindications, such as antipsychotics, opioids, testosterone, and several drugs used to treat cancer, acne, and multiple sclerosis.

In response to 15 years of safety information, in [2016](#) the FDA revised its initial REMS requirements for mifepristone. The changes included expansion of the gestational limit for treatment from 49 to 70 days, omission of the recommendation for in-person follow-up, and removal of a requirement that the prescriber be a physician. However, the requirement that the drug be dispensed by a certified provider remained intact.

In 2017, the [American Civil Liberties Union](#) (ACLU) filed a lawsuit, on behalf of a group of providers, challenging the REMS requirements for mifepristone. They cited low rates of complications associated with

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medical abortions and pointed to other drugs with more serious risks that did not carry REMS restrictions. The suit maintains that the REMS restrictions needlessly complicate access to the drug, particularly in rural or medically underserved areas. That case is still pending.

In 2019, a former FDA Commissioner published a [perspective](#) in the *New England Journal of Medicine* arguing the distribution restrictions imposed by the FDA were no longer appropriate given nearly two decades of use and evidence that mifepristone is extremely safe and effective.

And in response to the COVID-19 pandemic, the ACLU filed another lawsuit challenging the REMS requirement that mifepristone be dispensed in person. The court issued a [nationwide preliminary injunction](#) blocking part of the FDA's REMS restrictions on mifepristone when it is used for medication abortion, yet failed to suspend the restrictions when the medication is used for managing an early miscarriage. The temporary easing of the in-person requirements allows mifepristone to be mailed from health facilities to the patient where state law permits. The injunction will last for the duration of the litigation, or until the administration ends the federal public health emergency declaration.

POLICY IMPLICATIONS

The latest evidence of mifepristone's clinical and cost effectiveness adds an important perspective to the controversy surrounding its regulation and availability. REMS regulations were promulgated when existing safety data were scarce amid debates about medical abortion. But for women with early pregnancy loss, experts believe that restrictive regulations reduce access to now-recommended medical regimens to manage the process of miscarriage. The evidence on the clinical and cost effectiveness of mifepristone pretreatment is clear, and warrants a new look by FDA regulators. And in the midst of a pandemic, requiring in-person dispensing is a risk no woman with an early pregnancy loss should have to face.

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