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Ensuring Safe Access to Mifepristone During the Pandemic and Beyond

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Mifepristone (Mifeprex [Danco Laboratories]), 1 of 2 drugs used together to induce a medication abortion, was approved 20 years ago by the U.S. Food and Drug Administration (FDA) yet cannot be routinely prescribed and dispensed in the United States because it is covered by a risk evaluation and mitigation strategy (REMS) program. Imposed by the FDA, REMS programs are intended to minimize harms from special safety risks through such precautions as distribution controls, laboratory testing requirements, and a more robust process of informed consent. The REMS program for mifepristone is a successor to a pre-REMS restricted distribution scheme to reduce then-uncertain risks, such as major hemorrhage, from medication abortion. The program has the following 3 principal components: 1) it restricts distribution to clinics, medical offices, and hospitals; 2) it limits prescribing to certified prescribers attesting to their ability to diagnose gestational age and ectopic pregnancies, provide in-person counseling on safe use of the drug, and ensure access to surgical and medical care if needed; and 3) it requires that patients receive a special medication guide and sign an agreement acknowledging drug risks and receipt of counseling.

Although many health care providers have long called for reconsideration of the mifepristone REMS program, the coronavirus disease 2019 (COVID-19) pandemic has brought new attention to the issue, in part because of the risk of in-person visits. In May, the American College of Obstetricians and Gynecologists challenged the validity of the program, arguing that it impeded access and put patients at unnecessary risk for contracting the virus. In response to the challenge, a federal court in Maryland issued a preliminary nationwide injunction preventing enforcement of the mifepristone REMS program's requirements regarding dispensing and in-person counseling for the duration of the public health emergency on the grounds that they posed an undue burden by creating a substantial obstacle without conferring significant benefit. In reaching its ruling, the court noted that the FDA had already relaxed REMS-related restrictions on distribution for esketamine (Spravato [Janssen]) and natalizumab (Tysabri [Biogen]), as well as laboratory testing and imaging requirements for all REMS programs over the same period (1).

Disappointingly, the injunction has proved controversial. A month after the decision, the FDA applied for a stay to the Supreme Court, arguing that the restrictions on mifepristone do not pose an additional burden during the pandemic because surgical abortions remain available. More recently, claiming that the ruling demonstrates a movement toward deregulation and demedicalization, a group of Republican senators wrote a letter to the FDA commissioner urging him to exercise his authority to remove mifepristone from the market as an "imminent hazard to public health" (2).

As these legal battles unfold during the pandemic, it is worthwhile to revisit the validity of the mifepristone REMS program and the safety of the drug itself. Multiple groups, including a study group charged with reviewing the program (3), have documented low absolute risks for adverse events with mifepristone. One review reported that major complications occurred in fewer than 1% of women who used the drug (4). In addition, women in other countries without similar restrictions on mifepristone have not experienced major harms related to the drug (3). By contrast, the REMS requirements disproportionately threaten access for low-income patients and those from rural areas.

Examining the alternatives to mifepristone further bolsters the case for elimination of its REMS requirements. Guidelines from the FDA do not require a comparative safety analysis for a REMS determination (5). However, if the rationale for REMS programs is to ensure that the benefits of using a drug outweigh the risks, then alternatives to that drug—pharmacologic or otherwise—are relevant in the risk calculation. Women seeking an abortion have 2 options: a medication abortion using mifepristone or a surgical abortion.

By posing access barriers, the REMS requirements may lead women who struggle to obtain medication abortions—available through only 10 weeks of pregnancy—to seek later surgical abortions. A committee at the National Academies of Sciences, Engineering, and Medicine recently reviewed the safety and quality of abortion care. A key finding was that all methods of abortion are highly safe with only limited risks. Comparing medication versus surgical abortion in the first trimester, for example, the committee found similar risks for hemorrhage requiring blood transfusion (0.03% to 0.6% vs. 0% to 4.7%), infection (0.01% to 0.5% vs. 0% to 0.4%), and follow-up uterine aspiration (1.8% to 4.2% vs. <0.1% to 8%) (6). However, the risk for major complications from surgical abortion does increase with gestational age. One study found major complication rates of 0.16% for first-trimester surgical abortions and 0.41% for second-trimester or later procedures (7). Because the likelihood of having a surgical abortion increases once mifepristone is no longer an option, the REMS program may increase risk rather than reduce it.

Political developments have added urgency to calls for elimination of the mifepristone REMS program. Several states have passed laws with no health-based rationale that threaten women's constitutional right to abor-

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tion care, such as "heartbeat bills" that ban abortion after 6 weeks of pregnancy—before many women even know that they are pregnant. Some states have also enacted targeted regulation of abortion providers (TRAP) laws, which can require an abortion provider to obtain admitting privileges at a nearby hospital and may require clinics providing surgical abortions to comply with the requirements for ambulatory surgical centers. For example, one TRAP law in Texas caused approximately half of the state's clinics to shut down before it was deemed unconstitutional by the Supreme Court in 2016 (8). Despite this ruling, other states have continued to pass TRAP laws.

At the federal level, Justice Ginsburg's recent death has cast into doubt the precedent built since *Roe v. Wade*. Barriers to contraceptive access have also been erected, which may lead to more unintended pregnancies and, thus, abortions. In March 2019, the Trump administration unveiled a domestic "gag rule" preventing facilities from receiving federal grant money for family planning and preventive health services if they provide abortion referrals. An estimated 981 clinics left the Title X network, decreasing its capacity to provide contraceptive services by at least 46% (9). Subsequently, in July 2020, the Supreme Court upheld the expansion of exemptions for religious and moral reasons to the contraceptive mandate in the Patient Protection and Affordable Care Act, which may cause between 70 500 and 126 400 women to lose contraceptive coverage (10). Under policies that may simultaneously decrease access to abortions and increase demand for the procedure, unburdened access to mifepristone can help ensure timely access to abortion care, preventing adverse health effects.

The hostility toward reproductive rights in the United States also underscores the relevance of REMS messaging. During the pandemic, several states declared abortions to be "nonessential," signaling that abortion access is unimportant. Because REMS programs are mandated for drugs posing special risks, leaving any unnecessary REMS component in place suggests to women that a medication abortion is "unsafe" and could dissuade them from terminating their pregnancies using mifepristone. Given mifepristone's absolute and relative safety, continuing to keep the REMS in place resembles a value judgment rather than a factual evaluation of safety data.

After 20 years of safe experience with medication abortion, it is time for the FDA to release the REMS on mifepristone. Doing so would represent a meaningful step forward for women's health and the exercise of their constitutional rights.

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