

## Commentary

## Aligning mifepristone regulation with evidence: driving policy change using 15 years of excellent safety data

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Mifepristone was approved for sale in the United States 15 years ago this month. Use of mifepristone has steadily increased since its introduction; medical abortions now account for approximately 36% of the 1.1 million induced abortions that occur in the United States each year [1,2]. As clinical experience and research with mifepristone have expanded, the gold standard for medical abortion care has evolved beyond the protocol indicated in the FDA-approved label. Currently, the most common evidence-based protocols involve 200 mg mifepristone and 800 mcg misoprostol, and allow for use up to at least 63 days of gestation; these regimens are recommended by the World Health Organization [3], the American College of Obstetricians and Gynecologists and the Society of Family Planning [4] and the Planned Parenthood Federation of America [5]. The experiences of the hundreds of thousands of women who have had medical abortions using these protocols provide strong reassurance that mifepristone is extraordinarily safe; recent studies that include more than 423,000 women undergoing medical abortion with evidence-based regimens demonstrate that serious adverse outcomes are exceedingly rare [5–13].

Most complications associated with medical abortion are minor and include (but are not limited to) bleeding, cramping, fever and chills [9,13]. The outcomes of greatest clinical concern are heavy bleeding requiring transfusion, serious infection resulting in hospital admission, ongoing

pregnancy, undiagnosed ectopic pregnancy and death attributable to the medical abortion regimen. In one large study [5], 0.10% (238/233,805) of patients presented to the emergency department for treatment following medical abortion; another recent study found that that, in the majority of cases, when women sought care in emergency departments following medical abortion, the complications were typically minor and expected [13]. Rates of hospital admission due to any medical-abortion-related complications are extremely low, with reports ranging from 0.04% (6/13,373) to 0.3% (119/45,528) [5,11,12]. Bleeding is an expected consequence of medical abortion, and it is only in the most extreme of circumstances that women require transfusion to replace excessive blood loss. Recent studies report that blood transfusion was required in 0.03% (4/13,373) to 0.14% (16/11,319) of medical abortion patients [5,7,8,11,12]. Serious infection requiring hospitalization following medical abortion is also rare; recent estimates range from 0.01% (2/13,373) to 0.23% (26/11,319) [5,7,12,13]. Infection is more prevalent when misoprostol is administered through a vaginal, rather than an oral or buccal, route [14]. Five deaths have been attributed to septic shock associated with serious bacterial infections after using misoprostol vaginally [15,16], prompting the Planned Parenthood Federation of America to adopt new guidelines in 2006 that include buccal administration of misoprostol.

Ongoing pregnancy does not pose health risks to the woman *per se* but is important to monitor because surgical intervention may be required to complete the abortion and because misoprostol can be teratogenic [17,18]. However, medical abortion using mifepristone and misoprostol is highly effective, with recent studies reporting very low rates of ongoing pregnancy ranging from 0.13% (70/13,373) to 1.1% (499/45,528) [5,11–13].

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Ectopic pregnancy is a serious, but rare, event; ectopic pregnancies make up 1.3% to 2.0% of pregnancies in the United States [19,20]. Half of the pregnancies in the United States are unintended [21], and therefore, many women may not even be aware that they are pregnant, which could delay diagnosis of an ectopic pregnancy. However, women seeking abortion services, by definition, know that they are pregnant and may therefore be more likely to receive an early diagnosis of ectopic pregnancy. Furthermore, some studies show that rates of ectopic pregnancy are substantially lower among women seeking abortion services compared with overall rates in the general population [4,22,23].

Updated evidence-based regimens for medical abortion have increased options and lowered costs for women seeking abortion, all while maintaining an excellent safety profile. Research and practice in medical abortion continue to evolve, creating the potential to expand the medical option to even more women seeking abortion services. New studies demonstrate safe and effective use of mifepristone for medical abortion up to 70 days of gestation [24–26]. In addition, a growing body of research supports the safety of moving medical abortion away from clinic-centered models of care, allowing women to use mifepristone and misoprostol in the privacy and comfort of their home and to use technologies such as semiquantitative pregnancy tests to assess whether clinic follow-up is needed [27–29].

The current FDA-approved label for mifepristone limits its use to 49 days of gestation and indicates a 600-mg dose of mifepristone. In addition, mifepristone is not available in pharmacies; unlike other medications for which a doctor writes a prescription that the patient fills at a pharmacy, the prescriber's agreement specifies that mifepristone can be dispensed only in medical offices, clinics and hospitals. Furthermore, the FDA-approved label for mifepristone requires that patients make three office visits to receive the medications and complete extensive follow-up [30,31]. Although the safety and efficacy of updated evidence-based regimens for medical abortion are clear, some states require that providers follow the original FDA-approved protocol for medical abortion [32]. Requiring adherence to the FDA label does not serve the best interests of women; rather, it restricts the population of eligible women because of gestational age limits, directs women to take three times more mifepristone than evidence has shown to be necessary and requires that they make repeat visits to the clinic, demanding that increasing numbers of women travel great distances to receive services [33]. An extensive and rigorous literature supports the safety of both the current evidence-based regimens as well as innovative expanded protocols, providing a strong foundation for improving access to medical abortion by aligning the mifepristone label with the evidence.

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