Mifepristone: from the public eye to the reproductive endocrinology and infertility specialists' eye

Mifepristone is not a new drug and has multiple uses. France first approved mifepristone for use in 1988, and the Food and Drug Administration (FDA) in the United States did so in 2000. Mifepristone was initially used as a medical management option for termination of pregnancy. However, given its mechanism of action as a low-dose antagonist at the progesterone receptor and a high-dose antagonist at the glucocorticoid receptor, mifepristone is also used to treat hyperglycemia in Cushing syndrome, reduce fibroid size, and manage endometriosis and early pregnancy loss (EPL) (1).

In medical management of EPL up to 9 weeks, misoprostol alone can be used; however, mifepristone in combination with misoprostol has been shown to improve treatment efficacy in achieving complete expulsion of products (25% more efficacious) (2).

EPL is frequently encountered among reproductive endocrinology and infertility (REI) specialists. In their cross-sectional survey-based study, Anderson et al. (3) bravely investigated the preferred management strategies for EPL among REI specialists. They found that despite its superior efficacy, the mifepristone-misoprostol regimen was infrequently used—most likely due to barriers to accessing mifepristone.

This is not surprising because it takes more than a simple prescription and pharmacy visit for a patient to obtain mifepristone. As the investigators detail, the mifepristone Risk Evaluation and Mitigation Strategy (REMS) program is a set of FDA requirements enacted in 2007 with the original intent to monitor mifepristone use and reduce the risks of serious complications (1).

However, the requirements of REMS could also be considered onerous. The program has requirements for the following: prescribers (the requirements are certification under the program, completion of an agreement form, the ability to date pregnancies and diagnose ectopic pregnancies, and the ability to provide or refer for intervention if complications arise); patients (signing of an agreement form and copy of such form); and pharmacies (certification and pharmacy agreement form).

Additionally, before January 2023, the REMS program required certified providers to adhere to an "in-person dispensing requirement" and provide mifepristone directly to the patient (generally from their clinic or office). The providers generally obtained the mifepristone directly from the manufacturer (Danco) after registering with them as an ordering provider.

However, since January 3, 2023, certified pharmacies can dispense mifepristone directly to patients in person or by mail so long as the prescriber provides a copy of their REMS certification to that pharmacy. Again, this was not a simple change and was not popular in all corners because around that time, attorney generals in 20 states warned Consumer Value Store pharmacy and Walgreens that they could face legal consequences if they provided mifepristone by mail in those states.

Mifepristone has been no stranger to headlines of late. In 2023, the Supreme Court considered a case (*Food and Drug Administration v. Alliance for Hippocratic Medicine*) filed by groups questioning the FDA's approval, distribution, and safety protocols associated with mifepristone (4). Ultimately, the Supreme Court unanimously dismissed the case and upheld a lower court's ruling allowing continued access to mifepristone. The case has been held up as an emblematic of the tense standoff between state and federal regulations on reproductive health and the role of the law in shaping access to medical treatments.

Within this complex landscape, there has been confusion and lack of understanding of how medications such as mifepristone and misoprostol can be used to help manage EPL. Some pharmacists have reported that recent changes in state legal landscapes have meant pharmacies call prescriber offices to confirm the reasons for certain prescriptions, and thus, patients face delays in obtaining their medications (5).

Needless to note, much has changed since Anderson et al. (3) conducted their data collection in 2022, before the Dobbs decision. It is interesting that the investigators point that "ART pregnancies can vary from having 1 corpus luteum, multiple, or none depending on the cycle type," and it is possible that mifepristone may not be as effective for EPL management after in vitro fertilization. In any scenario, it is true that the assisted reproductive technology of medicine and EPL management has caught the public eye, and I applaud the investigators for bringing this nuanced subject to our REI readers' eyes.

CRediT Authorship Contribution Statement

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Declaration of Interests

V.M.A. has nothing to disclose.

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https://doi.org/10.1016/j.xfre.2024.08.008

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