Medical abortion reversal: science and politics meet

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Introduction

Medical abortion is safe, effective, and acceptable for patients seeking an early nonsurgical abortion. In 2014, medical abortions accounted for nearly one third (31%) of all abortions performed in the United States.[1] State-level attempts to restrict reproductive and sexual health have recently included bills that require physicians to inform women that a medical abortion is reversible. In this commentary, we will review the history, current evidence-based regimen, and regulation of medical abortion. We will then examine current proposed and existing abortion reversal legislation. The objective of this commentary is to ensure physicians are armed with rigorous evidence to inform patients, communities, and policy makers about the safety of medical abortion. Furthermore, given the current paucity of evidence for medical abortion reversal, physicians and policy makers can dispel bad science and misinformation and advocate against medical abortion reversal legislation.

History of medical abortion

Medical abortion typically refers to early pregnancy termination using abortion-inducing medications. An earlier regimen in the 1950s used oral aminopterin, a folic acid antagonist, to induce abortion in gestations <3 months.[2] However, it was the discovery of the abortifacient properties of natural prostaglandins, such as prostaglandin $E2_2$ and prostaglandin $F_{2\alpha}$, in the 1970s that propelled the use of medical abortion.[3] Prostaglandin analogs, such as gemeprost, sulprostone, and misoprostol, had more selective action on the myometrium and were effective for early abortion. Misoprostol, the most commonly used prostaglandin, binds to PGE_2 receptors in myometrial cells and causes contractions that ultimately lead to expulsion of the pregnancy.[4] However, their use continued to be limited by intolerable gastrointestinal side effects.[3]

In the United States, misoprostol alone is not approved for an abortion-related use, and is indicated by the US Food and Drug Administration (FDA) only for the prevention of gastric ulcers due to chronic nonsteroidal anti-inflammatory drugs.[5]

In 1980, researchers at Roussel-Uclaf, a French pharmaceutical company, developed mifepristone (RU-486), a competitive progesterone receptor antagonist. Mifepristone, a derivative of norethindrone, competitively binds to the intracellular progesterone receptor with 2.5-5 times higher affinity than progesterone without activating the receptor, which leads to endometrial decidual degeneration, cervical softening and dilatation, and release of and increased sensitivity to prostaglandins.[4] While mifepristone alone was found to be only 60-80% effective in achieving complete abortion, the combination of mifepristone and lower doses of prostaglandin analog improved the efficacy to nearly 100%.[6] In 1988, RU-486 was approved for early medical abortion in France. However, the FDA imposed an import ban on the drug in 1989. In the early 1990s, research in the United States focused on alternative regimens such as low-dose methotrexate with misoprostol while a large clinical trial involving 16,369 women across 300 centers demonstrated a 95.3% rate of complete abortion following mifepristone and a prostaglandin analog.[3,7] In 2000, the FDA approved mifepristone for early medical abortion in the United States with the following regimen: mifepristone 600 mg orally followed by misoprostol 400 μg orally 48 hours later up to 49 days' gestation from last menstrual period.[8]

Current evidence-based medical abortion regimen

Medical abortions typically employ a 2-drug regimen: mifepristone followed by a prostaglandin analog. Although mifepristone or misoprostol are sometimes used alone, the combined regimen is preferred, as it has demonstrated significantly greater efficacy.[4,9] Many studies have explored the timing, dosing, and side effects of mifepristone-misoprostol regimens. The current evidence-based regimen demonstrated comparable efficacy (95-99%) with fewer gastrointestinal side effects and up to higher gestational ages. In 2016, the FDA approved a new label for mifepristone that included an updated protocol.[8] This protocol reflected a regimen supported by the American Congress of Obstetricians and Gynecologists (ACOG), Society of Family Planning, National Abortion Federation, and Planned Parenthood Federation of America: mifepristone 200 mg orally in a clinical setting followed by misoprostol 800 μg self-administered buccally 24-48 hours later at home up to 70 days' gestation. Although an off-label use, misoprostol may also be administered vaginally 6-8 hours following mifepristone.[8,10-13] The 2016 FDA label not only included a more effective dosing regimen but included changes that expanded the gestational limit from 49-70 days, removed the recommendation of in-person follow-up, did not require a physician prescriber, and no longer required the reporting of nonfatal adverse events.[8]

Regulation and restriction of medical abortion

Although medical abortion is safe, effective, and acceptable, there remain restrictions that target medical abortion. While the 2016 FDA label for mifepristone included many sweeping

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changes, no major changes were made to its Risk Evaluation and Mitigation Strategy (REMS). A REMS is a set of restrictions beyond the drug label that addresses the specific risks of a given drug. Mifepristone's REMS requires that the drug by dispensed in clinics, medical offices, and hospitals under the supervision of a certified prescriber; health care providers must become certified by the drug distributor; and each woman must be given an FDA-approved medication guide and sign FDA-approved consent.[14] Given the documented safety and effectiveness of mifepristone, this federal mandate only serves to restrict access to the drug, rather than mitigate any specific serious risk from mifepristone.

At the state level, many states have enacted laws that impedes the provision of medical abortion. In all, 34 states require that only licensed physicians can prescribe a medical abortion even though evidence demonstrates the competency of midlevel clinicians—such as nurse-midwives, nurse practitioners, and physician assistants—in providing all aspects of medication abortion.[15,16] For women living in remote areas, telemedicine for medical abortion not only improves access to medical abortion but also reduces second-trimester abortions.[17] Although the provision of medical abortion by telemedicine compared to in-person provision is equally effective, safe, and acceptable to both patients and providers, 19 states require that a physician must be physically present for mifepristone administration.[15,18,19]

There are also state-level attempts to require physicians to inform women that a medical abortion is reversible (Table). Since 2015, legislators in 9 states have introduced medical abortion reversal bills. In South Dakota and Utah, women must be informed that mifepristone alone does not always end a pregnancy. In Arkansas, women must be informed that "it may be possible to reverse the effects of the abortion if the pregnancy woman changes her mind." In Arizona, a law passed in 2015 that required counseling on medical abortion reversal, but it was repealed 2016. Similar bills were

TABLE
Status of medication reversal bills and statutes by state, bill number, and most recent action on bill[20-32]

State bill no.	Status	Overview
Arizona SB 1318	Enjoined	• State legislators introduced bill in February 2015 requiring physicians to tell women seeking drug-induced abortions that procedure may be reversible. • Law was passed in March 2015. • Planned Parenthood challenged law in federal District Court. • Court blocked law in August 2016.
Arkansas HB 1578	Enacted	• State legislators introduced bill in March 2015 requiring physicians to tell women seeking drug-induced abortions that procedure may be reversible. • Law was enacted in April 2015.
Colorado HB 1086	Failed to pass	• In January 2017, legislators introduced bill mandating that physician prescribing or administering abortion-inducing drugs must inform woman orally and in person that it may be possible to reverse abortion. • Bill required that physician provide hard copies of state-prepared materials on abortion reversal and direct woman to online versions. • Failure to comply would result in possible civil penalties and professional disciplinary action under Colorado medical malpractice law. • Final activity was in February 2017 when bill did not pass.
Georgia SB 239	Proposed; no further movement	• State legislators introduced bill in February 2017 mandating that health care providers tell women seeking chemical abortions that procedure may be reversible but that "time is of the essence" at least 24 h prior to abortion. • It also required abortion reversal information be available on state website. • There was no further movement on bill prior to end of legislative session.
Idaho SB 1131	Proposed; no further movement	• In March 2017, legislators introduced bill requiring Department of Health to provide information and assistance on locating health care providers who will consult women on "the interventions, if any, that may affect the effectiveness or reversal of a chemical abortion." • Bill mandated maintenance of weekly monitored "stable Internet website" with this information. • It required health care providers contacted by pregnant patients for abortion services to provide them website's address. • Final activity was in March 2017 when bill died without hearing at end of legislative session.

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