

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 and prostaglandin F_{2α}, 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 PGE₂ 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 be 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 impede 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 bill²⁰⁻³²

State bill no.	Status	Overview
Arizona SB 1318	Enjoined	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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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(continued)

TABLE

Status of medication reversal bills and statutes by state, bill number, and most recent action on bill²⁰⁻³² (continued)

State bill no.	Status	Overview
Indiana HB 1128	Proposed; passed House; referred to Senate Committee on Judiciary with no further movement	<ul style="list-style-type: none"> • In January 2017, legislators introduced bill stipulating that before drug-induced abortion, woman must be informed verbally and in writing that it may be possible to arrest or reverse abortion. • Fiscal impact statement attached to bill noted, "If a federal lawsuit would be filed and the plaintiffs prevail on claims that the statute violated constitutionally protected civil rights, the state would be required to pay the legal bills of the plaintiffs. In 2013 and 2015, Indiana paid the ACLU legal fees for similar types of cases in the amount of \$170,342 and \$122,945 respectively." • In March 2017, bill was referred to Committee on Judiciary.
North Carolina HB 62	Proposed; referred to House Committee on Health with no further movement	<ul style="list-style-type: none"> • A bill introduced in 2017 through 2018 legislature session stipulated that immediately prior to administering mifepristone, provider must inform woman that it is possible to discontinue abortion by not taking misoprostol and taking progesterone to counteract mifepristone. • Bill requires Department of Health and Human Services website to include information on how, where, and from whom woman can receive assistance discontinuing drug-induced abortion. • Bill requires that provider present "medical proof to the woman that fetal death has occurred" prior to administering misoprostol. • Bill was referred to Committee on Health in February 2017, with no further movement since.
South Dakota HB 1157	Enacted	<ul style="list-style-type: none"> • In January 2016, legislators introduced bill requiring physicians to tell women seeking drug-induced abortions that woman can discontinue drug-induced abortion after taking mifepristone but not taking misoprostol. • It requires Department of Health website to include information on discontinuing drug-induced abortion. • Bill was signed into law in March 2016.
Utah HB 141	Enacted	<ul style="list-style-type: none"> • In January 2017, legislators introduced bill requiring "specified medical personnel to inform a woman seeking an abortion of the options and consequences of aborting a medication-induced abortion." • It requires Department of Health to maintain published and printed materials of this information. • Bill was signed into law in March 2017.

ACLU, American Civil Liberties Union; HB, House Bill; SB, Senate Bill.

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debated in Colorado, Indiana, Idaho, North Carolina, and Georgia.²⁰⁻³²

Medical abortion reversal

The purported mechanism of medical abortion reversal centers on high-dose progesterone supplementation after taking mifepristone and before misoprostol administration. There are currently only 2 published studies on medical abortion reversal: a case series and a systematic review of first-trimester medical abortion reversal.^{33,34} The American Medical Association and ACOG have voiced concerns about the medication abortion "reversal" process, stating that "there is no credible, medical evidence" supporting its efficacy.³⁵

In the case series by Delgado and Davenport,³³ 7 women received varying regimens of intramuscular, oral, and/or vaginal progesterone treatment after taking an unknown dose of mifepristone for medical abortion at 7-11 weeks' gestation.

Prior to taking progesterone, at least 5 cases had a documented living embryo. Of the 6 patients with follow-up data, 4 continued the pregnancy to term without apparent anomalies (67%; 95% confidence interval, 30–90%), and 2 had abortions within 3 days of taking mifepristone. Based on this case series, Delgado and Davenport³³ recommend the following protocol for medical abortion reversal: ultrasound or human chorionic gonadotropin levels to confirm embryonic/fetal viability and progesterone 200 mg intramuscularly daily for 3 days, then every other day until day 13 after mifepristone, and finally twice weekly until the end of the first trimester. Delgado and Davenport³³ concluded that progesterone's competitive antagonism of mifepristone can reverse a medical abortion. However, there are many limitations to their case series: small sample size, lack of long-term follow-up, as well as no review or oversight by an institutional review board or ethics committee. The authors did not report

how many women sought medical abortion reversal but were excluded due to embryonic demise or incomplete abortion.

In the systematic review conducted by Grossman et al,³⁴ the purpose was to review the literature on reversal of medical abortion as well as continuing pregnancy after mifepristone. Only the case series of Delgado and Davenport³³ met inclusion criteria of medical abortion reversal, and 13 studies were included on continuing pregnancy following the use of mifepristone alone for first-trimester medical abortion. The continuing pregnancy proportions ranged from 8-46% with the different regimens. Continuing pregnancy was more common with lower mifepristone doses and higher gestational age. The systematic review found “no credible evidence that using medication after mifepristone is better than expectant management in a continuing pregnancy and suggesting otherwise is scientifically untenable.”³⁴

Possible unintended consequences of medical abortion reversal bills

Medical abortion reversal bills are not based in science and can lead to unintended consequences. Controversial state legislation can produce substantial litigation costs for taxpayers. This was clearly demonstrated in *Whole Women's Health v Hellerstedt*,³⁶ the Supreme Court case that challenged Texas House Bill 2,³⁷ which placed a series of restrictions on abortion clinics within the state. After the restrictions were struck down by the Supreme Court in June 2016, the Center for Reproductive Rights filed a \$4.5 million lawsuit to recuperate legal fees from the state of Texas.³⁸ Similarly, the state of North Carolina had to use \$1 million of its emergency fund for legal fees defending an abortion ultrasound law that required health care providers to narrate ultrasound images to women and was also ultimately struck down.³⁹

Abortion reversal legislation forebodes a number of adverse consequences beyond simply its potential financial repercussions. Women could decide to start a medical abortion before they are certain about their decision since they are told they can reverse it. Counseling about medical abortion reversal undermines the abortion counseling process. In states with abortion reversal legislation, women are in effect being conscripted into an unmonitored research project (since, as of now, there has been no documentation of abortion reversal therapy being administered under an institutional review board—approved protocol). This undermines a vast corpus of ethical standards and regulation governing human subjects research and poses a direct threat to these women's health. Furthermore, it is a dangerous intrusion into the physician-patient relationship to force doctors to tell their patients about an unproven therapy.

Conclusion

An established and growing body of evidence-based literature supports the safety, effectiveness, and acceptability of medical abortion whereas medical abortion reversal remains unsubstantiated. Efforts to mandate that physicians inform women about this medically unproven therapy not only pose risks to

women's health but also undermine the physician-patient relationship. Given the current paucity of evidence for medical abortion reversal, it is the responsibility of physicians and obstetrician-gynecologists to advocate for our patients and oppose medical abortion reversal bills. ■

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ABSTRACT

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