

House Committee on Health and Human Services
February 20, 2019
Written Opposition to House Bill 2274
From
Daniel Grossman, MD
University of California at San Francisco
Director, Advancing New Standards in Reproductive Health (ANSIRH)

Abortion “Reversal” — Legislating without Evidence

Daniel Grossman, M.D., and Kari White, Ph.D., M.P.H.

Women up to 10 weeks pregnant who are having a medication abortion generally take one dose of mifepristone, which blocks the progesterone receptor, followed within 48 hours by a dose of misoprostol, a prostaglandin that causes cervical dilation and uterine contractions, leading to expulsion of the pregnancy tissue. Four states (Arkansas, Idaho, South Dakota, and Utah) require abortion providers to tell their patients about treatment that may reverse the effect of mifepristone if they change their mind after starting a medication abortion. So-called abortion reversal involves administering repeated doses of progesterone. Since 2017, other states have proposed similar bills and the California Board of Registered Nursing approved a course on medication-abortion reversal for continuing-education credit. This trend is troubling because of the lack of medical evidence demonstrating the safety and efficacy of the treatment; laws promoting it essentially encourage women to participate in an unmonitored research experiment.

When states began passing laws on abortion reversal, the only published report on this treatment was a case series involving seven patients. A systematic review we coauthored in 2015 found no evidence that pregnancy continuation was more likely after treatment with progesterone as compared with expectant management among women who had taken mifepristone.¹ Our review found that the proportion of continuing pregnancies after mifepristone alone varied from 8% to 46% in published studies.

Recently, Delgado et al. published a case series involving 754 patients who underwent reversal treatment in the United States and several unnamed countries.² After excluding 27% of patients for various reasons, they report that 47% had a live birth. The authors conclude that reversal treatment is effective, citing the higher proportion of continuing pregnancies in their study as compared with a historical control rate of 25% of women who had continuing pregnancies after taking mifepristone alone. This estimate comes from Maria et al., the only published report that examined rates of pregnancy continuation after a single 200-mg dose of mifepristone,³ which is the dose most commonly used in current medication-abortion regimens. This study, which included 30 women who were up to 7 weeks pregnant, 25 of whom were no more than 6 weeks pregnant, found that 23% had continuing pregnancies 7 days later.

It is difficult to compare the results from Delgado et al. with data on mifepristone alone for several reasons. In the Delgado study, some providers performed ultrasonography in patients presenting for reversal and excluded those found to have embryonic death. These patients were removed from the denominator of the proportion of women with continuing pregnancies, which could have contributed to the higher success rate for reversal treatment — especially at gestational ages of more than 6 weeks, when cardiac activity is more apparent. In addition, the authors excluded patients who were lost to follow-up before 20 weeks, which probably exaggerated the treatment’s reported success.

Gestational ages in Delgado et al. (up to 9 weeks) also differed from those in Maria et al. As Delgado et al. note, pregnancy continuation is more common with advanced gestation; therefore, it is important to compare groups of similar gestational age. We analyzed the effectiveness of reversal treatment by comparing rates of continuing pregnancy among women who were up to 6 or 7 weeks pregnant in the two studies.

Among women who were up to 6 weeks pregnant, 38% (95% confidence interval [CI], 31 to 45) of those who received reversal therapy had a continuing pregnancy.² This proportion was not significantly different from the 20% (95% CI, 9 to 39) of women who had a continuing pregnancy after taking mifepristone alone ($P = 0.119$).³ The rates of pregnancy continuation were also not significantly different when we included women who were up to 7 weeks pregnant, despite the fact that the reported success rate for reversal therapy was most likely an overestimate at 7 weeks because some patients were excluded from treatment after ultrasound screening for

embryonic viability. Because there are no published data on rates of pregnancy continuation after a 200-mg dose of mifepristone alone at more than 7 weeks' gestation, we cannot evaluate the effectiveness of reversal treatment beyond this gestational age.

The safety data presented by Delgado et al. are minimal. No adverse events were reported among pregnant women, but it is unclear whether such data were routinely collected. The reported data on birth defects and preterm birth are generally reassuring; given the range of progesterone regimens used and the lack of reporting by regimen, however, it is difficult to draw conclusions about the treatment's safety. Data from a registry in France suggest that exposure to mifepristone alone does not increase the risk of birth defects.⁴

Equally unclear is the demand for reversal treatment. Since participants in the study by Delgado et al. were recruited from several unnamed countries over a period of 4 years, it is impossible to estimate what proportion of patients undergoing medication abortion is represented by this sample. According to data obtained from Danco Laboratories, the U.S. manufacturer of mifepristone, less than 0.004% of patients who took mifepristone between 2000 and 2012 ended up deciding to continue their pregnancies.¹ Other research indicates that decisional certainty among women having an abortion is high — and higher than it is among patients making other decisions about medical treatment.⁵

Still, efforts should be made at the time of preabortion counseling to identify women who may be conflicted and to provide additional support to help them make an informed decision. Allowing patients to take mifepristone at home, which has been permitted since the drug's label was updated in 2016, may reduce the already small number of women who change their mind by giving patients more control over where and when they take the medication. But for patients who do change their mind after taking mifepristone, what is the best course of action? If a woman changes her mind within an hour after taking the drug, vomiting should be induced. Beyond that time frame, we believe the pregnancy should be carefully followed.

One could argue that the demand for abortion reversal treatment is so low that additional research is not justified. But if researchers do perform additional studies, it is critical that such studies be rigorously designed and conducted in an ethical manner. Clinical equipoise exists for this question, since there is no evidence that treatment is superior to doing nothing. In such cases, a randomized, placebo-controlled trial is the most appropriate study design. For now, any use of reversal treatment should be considered experimental and offered only in the context of clinical research supervised by an institutional review board (IRB). Delgado et al. obtained IRB approval for their retrospective data analysis, but it is not clear that approval was obtained in advance for their experimental treatment protocol. In fact, the study was retracted temporarily because of concerns raised about what the authors initially described as an IRB "waiver."

We believe that states' mandating that health care providers give patients information about an unproven and experimental therapy is a disturbing intrusion into the relationship between physicians and their patients. Additional states will undoubtedly consider such legislation, despite the lack of evidence for abortion reversal treatment. We should all be concerned when politicians recommend treatment options over the advice of medical professionals.

Disclosure forms provided by the authors are available at NEJM.org. From *Advancing New Standards in Reproductive Health*, Bixby Center for Global Reproductive Health, and the Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (D.G.); and the Department of Health Care Organization and Policy, School of Public Health, University of Alabama at Birmingham (K.W.).

1. Grossman D, White K, Harris L, et al. Continuing pregnancy after mifepristone and "reversal" of first-trimester medical abortion: a systematic review. *Contraception* 2015; 92: 206-11.

2. Delgado G, Condy SJ, Davenport M, et al. A case series detailing the successful reversal of the effects of mifepristone using progesterone. *Issues Law Med* 2018; 33: 3-14.

3. Maria B, Chaneac M, Stampf F, Ulmann A. Early pregnancy interruption using an antiprogestosterone steroid: Mifepristone (RU 486). *J Gynecol Obstet Biol Reprod (Paris)* 1988; 17: 1089-94. (In French.)

4. Bernard N, Elefant E, Carlier P, et al. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. *BJOG* 2013; 120: 568-74.

5. Ralph LJ, Foster DG, Kimport K, Turok D, Roberts SCM. Measuring decisional certainty among women seeking abortion. *Contraception* 2017; 95: 269-78.