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The Court's approach in *NIFLA*, as the dissent noted, "could radically change prior law, perhaps placing much securities law or consumer protection law at constitutional risk." Many health

 An audio interview with Prof. Parmet is available at NEJM.org

laws could be similarly threatened. Already a lower court

has preliminarily enjoined Food and Drug Administration warning labels for cigars on the basis

of *NIFLA*.<sup>5</sup> Whether that injunction holds, and whether other health laws will be struck down on First Amendment grounds, remains to be seen. What is clear is that the Court has created new uncertainty, and invited new litigation, regarding numerous health laws that were once assumed to be constitutional.

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From Northeastern University School of Law, Boston (W.E.P.); the College of Public

Health and the Moritz College of Law, Ohio State University, Columbus (M.L.B.); and California State University, East Bay, Hayward (J.A.S.).

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## 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.<sup>1</sup> 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.<sup>2</sup> 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,<sup>3</sup> 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.

Percentage of Women with Continuing Pregnancies after Taking 200 mg Mifepristone with or without Progesterone.*				
Treatment	Total No. of Pregnancies	Continuing Pregnancies	Percentage of Continuing Pregnancies (95% CI)	P Value
Gestational age ≤6 wk				
Mifepristone followed by progesterone	189	71	38 (31–45)	0.119
Mifepristone alone	25	5	20 (9–39)	
Gestational age ≤7 wk				
Mifepristone followed by progesterone	291	121	42 (36–47)	0.076
Mifepristone alone	30	7	23 (21–41)	

\* Data are from Delgado et al.<sup>2</sup> and Maria et al.<sup>3</sup> Maria et al. report a total of seven continuing pregnancies in the sample of 30 women who were 7 weeks pregnant or less. There were two abortion failures among the five women who were between 6 and 7 weeks pregnant, but whether these were continuing pregnancies is unclear. We therefore made the conservative assumption that five of the seven continuing pregnancies occurred among the 25 women who received mifepristone at 6 weeks' gestation or less and that the two failures that occurred among those who were between 6 and 7 weeks pregnant were both continuing pregnancies.

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.<sup>2</sup> 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 ( $P=0.119$ ) (see table).<sup>3</sup> 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.<sup>4</sup>

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 mife-

pristone between 2000 and 2012 ended up deciding to continue their pregnancies.<sup>1</sup> 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.<sup>5</sup>

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.

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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.).

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## Extensively Drug-Resistant Typhoid — Are Conjugate Vaccines Arriving Just in Time?

Jason R. Andrews, M.D., Farah N. Qamar, F.C.P.S., Richelle C. Charles, M.D., and Edward T. Ryan, M.D.

In Hyderabad, Pakistan, an outbreak of extensively drug-resistant (XDR) *Salmonella enterica* ssp. *enterica* serovar Typhi, resistant to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins, was recognized in November 2016 and has now spread to Karachi, home to more than 14 million people. More than 1000 cases have been confirmed by blood culture; since most typhoid cases are treated empirically, however, the true number of cases is probably many times greater. The outbreak is being caused by the H58 clade, a multidrug-resistant haplotype of *S. Typhi* that is common in Asia and areas of Africa. The H58 *S. Typhi* involved in the outbreak contains a chromosomally inte-

grated antimicrobial-resistance cassette imparting resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole, and the XDR variant also contains an IncY plasmid that carries not only the fluoroquinolone-resistance gene *qnrS* but also the CTX-M-15 gene *bla* that mediates resistance to ceftriaxone.<sup>1</sup> *S. Typhi* already causes invasive disease in 12 million to 22 million people each year, many of whom live in South and Southeast Asia, and the emergence of an XDR variant in this densely populated area is extremely worrisome.<sup>2</sup>

Prior to the advent of antimicrobial therapy, case fatality rates for typhoid fever exceeded 20% in many areas, since untreated disease led to complications such as intestinal perforation. In 1948, the

first effective antimicrobial therapy for typhoidal salmonella, chloramphenicol, ushered in a new era in the management of enteric fever (see timeline). Within 2 years, however, the first clinical isolate resistant to chloramphenicol was reported. But resistance was relatively uncommon, and chloramphenicol remained the mainstay of therapy for the next two decades. In the early 1970s, outbreaks of chloramphenicol-resistant typhoid with evidence of horizontal transfer of resistance genes were reported around the world. Ampicillin and trimethoprim-sulfamethoxazole emerged as alternative, albeit possibly inferior, therapies for chloramphenicol-resistant enteric fever. By the late 1980s, resistance to all three antibiotics (multidrug-resistant typhoid) was increasingly