



Fatal Infections Associated with Mifepristone-Induced Abortion

Michael F. Greene, M.D.

Related article, p. 2352

The Population Council submitted a new drug application to the Food and Drug Administration (FDA) on March 14, 1996, for the progesterone antagonist mifepristone (also known as RU 486) to be

used as an abortifacient. The application was based on two studies, involving a total of 4600 women, of the drug's safety and efficacy in the termination of early pregnancies. Four years later, a review article in the *Journal*¹ cited 14 studies of mifepristone with more than 300 patients per study and a total of 26,000 treated women. By the summer of 2000, mifepristone had been used to treat more than 500,000 women in nearly a dozen countries in which it had been licensed. The FDA approved the drug for use in the United States on September 28, 2000, after more than 80 supplemental filings and submissions by the sponsor in response to queries from the agency. Mifepristone was one of 18 new molecular entities approved by

the agency that year. Its 54-month approval time contrasted with the median total approval time of 15.6 months for all new molecular entities approved that year.

That original approval included a "black-box" warning that use of the drug could result in incomplete abortion requiring surgical intervention. It advised prescribers to be sure that appropriate provisions were made to provide that care when needed. On November 15, 2004, the FDA strengthened the warning in the black-box labeling of mifepristone to call attention to potentially fatal complications (ruptured ectopic pregnancy and septic shock) associated with its use in terminating early pregnancies. At the same time, the agency updated its Web site ([\[www.fda.gov/cder/drug/infopage/mifepristone/default.htm\]\(http://www.fda.gov/cder/drug/infopage/mifepristone/default.htm\)\) to reflect the deaths of three U.S. women who had taken the drug since its introduction in the United States; one of these deaths was due to a ruptured ectopic pregnancy, and two were due to septic shock. This updating occurred during the same week that FDA officials were called before a congressional committee investigating the high-profile withdrawal of rofecoxib \(Vioxx\) in order to respond to charges of lax oversight of the drug industry. Some used the circumstances to call for the withdrawal of mifepristone on the grounds that it, too, posed an undue safety risk.](http://</p></div><div data-bbox=)

On July 19, 2005, the agency reported that it was aware of four U.S. deaths due to sepsis in women who had used mifepristone and announced its second revision to the black-box warning in eight months. This revision named *Clostridium sordellii* as responsible for

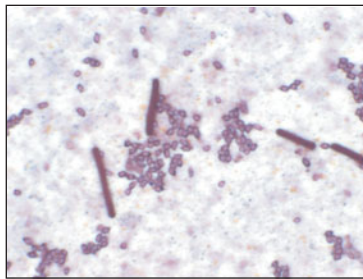
two of the deaths and specifically called attention to the somewhat unusual and rather distinctive signs and symptoms associated with these infections — an absence of fever but the presence of refractory hypotension, hemoconcentration, effusions in multiple serous cavities, and dramatic leukocytosis. A Canadian woman is also known to have died in 2001 of the same bacterial infection under similar circumstances.

These deaths have important implications both for the care of individual patients and for public policy. Disturbing aspects of the cases described by Fischer et al. in this issue of the *Journal* (pages 2352–2360) include the following: all the women were young and healthy; they had apparently successful procedures (there was no evidence on autopsy of retained products of conception); their clinical presentations were somewhat cryptic because they had cramping, which is very common after the procedure, and no fever; and they all died remarkably rapidly after presentation. The efforts of the FDA and the Centers for Disease Control and Prevention to post information about these deaths on their Web sites, a “Dear Health Care Provider” letter from the manufacturer, publication of a “Dispatch” in the *Morbidity and Mortality Weekly Report*,² and the article by Fischer et al. will all help to alert clinical care providers to this potentially lethal syndrome.

Inevitably, the public health question of the safety of this method of pregnancy termination must be addressed. Some critical questions are: How great is the risk? With what is it appropriate to compare this risk? And what are the alternatives?

The manufacturer reports that “more than 460,000” procedures

have been performed in the United States since the drug’s approval. There is some uncertainty about this number because, although the manufacturer knows how many tablets it has shipped, it is not absolutely certain how many procedures have been performed with those tablets. The FDA-approved dose per procedure



Clostridium sordellii.

is three 200-mg tablets (600 mg total), and the tablets are packaged three to a pack. But on the basis of substantial evidence of equivalent safety and efficacy, the World Health Organization has recommended a dose of 200 mg per procedure. Most providers, including large institutional providers such as Planned Parenthood of America, routinely use the 200-mg dose. The manufacturer’s estimate of 460,000 procedures is based on the assumption that most entail use of the lower dose. These figures would suggest that the risk of death from infection is less than 1 per 100,000. In the United States, the risk of death from any cause associated with attempting to carry a pregnancy to term is 8 to 10 times that.

The more appropriate comparison, however, is with the risk associated with other methods of inducing abortion. The overall maternal mortality rate associated with induced abortion in the United States is approximately 1 per 100,000. That overall rate is a “blended” rate including all the procedures performed in the

United States at all gestational ages. The gestational-age-specific rate increases exponentially from 0.1 per 100,000 at 8 weeks’ gestation to 8.9 per 100,000 at 21 or more weeks’ gestation. Mifepristone is approved for the termination of pregnancies at less than seven weeks’ gestation. Therefore, the appropriate comparison is with a risk of 0.1 per 100,000 for surgical abortions performed at less than eight weeks’ gestation.

As tragic as the deaths of these young, healthy women are, they remain a small number of rare events without a clear pathophysiologic link to the method of termination. Patients should be informed of this risk before they consent to the procedure and should be vigilant for symptoms after the procedure. Providers must be aware of this potential complication and not be reassured by the absence of fever. Regulators should keep this rare complication in perspective and not overreact to scant data by prematurely foreclosing the only approved medical option for pregnancy termination. It may be difficult, however, to maintain equipoise on this issue in the wake of recent perceived regulatory lapses and amid the turbulence created by any discussion about abortion.

An interview with Dr. Greene can be heard at www.nejm.org.

Dr. Greene is a professor of obstetrics, gynecology, and reproductive biology at Harvard Medical School, Boston, director of obstetrics at Massachusetts General Hospital, Boston, and an associate editor of the *Journal*.

1. Christin-Maitre S, Bouchard P, Spitz IM. Medical termination of pregnancy. *N Engl J Med* 2000;342:946-56.
2. *Clostridium sordellii* toxic shock syndrome after medical abortion with mifepristone and intravaginal misoprostol — United States and Canada, 2001–2005. *MMWR Morb Mortal Wkly Rep* 2005;54:724. (Also available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5429a3.htm>.)