Mortality in Perspective: Mifepristone-Misoprostol Medical Abortion

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During recent months, the number of deaths attributable to medical abortion with mifepristone and misoprostol has raised much concern among government regulators, Congress, and healthcare providers in the United States. Exactly which component of the medical abortion was the cause has been a source of much speculation. Despite the ease with which such speculation has been offered and, in some cases, acted upon, the evidence for each putative cause must still be considered. The mortality risk associated with medical abortion is similar to that of spontaneous abortion and is much lower than that of childbirth itself. And, what risk does exist more likely is attributable to social and policy-related issues that exist only in the United States than to the medical abortion process itself.

Seven deaths coinciding with medical abortion have been reported since 2001, 4 of which were related to infection with a rare organism, *Clostridium sordellii*.[1] Two of these deaths were recently reported; one has been clearly deemed to be unrelated to the medical abortion, and the other is still under investigation. One other temporally related death was found not to be attributable to the medical abortion. Several organizations including the US Food and Drug Administration (FDA) have voiced concern that differences in medical abortion regimens may explain some of these deaths. The vast majority of women undergoing medical abortions and all of the women who died did not use the regimen approved by the FDA. However, to understand the risks of medical abortion, it is important to first understand the specifics of the regimens, to put the risks into perspective, and to understand what other factors might be related—beyond the medications themselves.

Approved and "Off-Label" Regimens

For a woman electing to terminate a pregnancy, medical abortion offers a nonsurgical option. For many women this may be more acceptable for any number of personal, cultural, or other reasons. In September 2000, the US FDA approved a regimen to be administered up to 49 days' gestation that consists of 600 mg of mifepristone (a progesterone antagonist) followed 36 to 48 hours later by 400 µg of misoprostol (a prostaglandin analogue) taken orally. Women must return to the office 2 days after taking the mifepristone to receive the misoprostol tablets. Confirmation of pregnancy expulsion occurs approximately 2 weeks later. In clinical practice, similar regimens in Europe and China have had a long history of safe clinical use without any reported deaths due to infection. However, the meticulousness of monitoring and the reliability of reporting, especially in China, are unclear.

Among published trials, more women have received a regimen of 200 mg mifepristone and vaginal misoprostol than have received the US FDA-approved regimen of 600 mg mifepristone and oral misoprostol, and the US FDA-approved regimen is, in fact, less stringently evaluated than some other evidence-based regimens. Such "off-label" use of medications frequently becomes the standard of care when there is sufficient evidence that the off-label use is effective and has benefit for the patient. Most obstetrician/gynecologists are quite comfortable with off-label use, as few of the commonly used medications are approved for their obstetrics applications (eg, magnesium sulfate, terbutaline, or indomethacin for preterm labor). In the United States, the most common alterations to the US FDA-approved regimen for medical abortion include:

- Use of mifepristone 200 mg;
- Use of misoprostol 800 µg vaginally;
- Decreasing the time interval between the drugs to 6 to 24 hours;
- Use of the mifepristone-vaginal misoprostol regimen through 63 days of gestation;
- Providing the misoprostol to the patient at the same time as the mifepristone, to be administered at home by the patient; and
- Follow-up in 1 week with vaginal ultrasound confirmation of pregnancy expulsion.

The evidence indicates that these changes increase efficacy, decrease side effects, and improve the acceptability of medical abortion to women primarily by decreasing the time interval to successful abortion.[2] The risk of infection is similar, if not lower, in studies using evidence-based regimens (0.21%,[3] 0.28%[4]) compared to that in the US FDA-approved regimen (0.47%[5]).

Reporting of abortion procedures and complications is a passive process in the United States, which often meets resistance both at the provider level and the state level; in fact, 3 states (Alaska, California, and New Hampshire) do

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not provide abortion data to the Centers for Disease Control and Prevention. Reporting is further complicated by the social environment in the United States, which can make it more likely for women not to report having had an abortion.[6] Accordingly, we cannot be certain of the true incidence of serious complications and death with early abortion, whether performed surgically or with medicines. As with any new treatment, especially a politically contentious one, serious complications are more likely to be reported. Nevertheless, such problems appear to be very rare.

By the best estimates for the United States, the following are the mortality risks per 1 000 000 women for various health states:

- Surgical abortion overall[7,8]: 6–11
- Surgical abortion through 63 days' gestation[7]: 0.4–2
- Medical abortion through 63 days' gestation[9]: 2–24
- Spontaneous abortion[8,10]: 9–15
- Term delivery[8,11]: 70–120
- Motor-vehicle–related mortality, annual[12]: 160
- Total mortality for 20-year-old women, annual[13]*: 454
- Total mortality for 30-year-old women, annual[13]*: 632

(*All-cause mortality, including pregnancy-related and motor-vehicle–related mortality.)

As reflected by the wide range in the estimates, estimates of early pregnancy mortality are difficult to define precisely because of the small number of deaths and difficulty determining the denominators. Importantly, we have no evidence to allow comparison of different medical abortion regimens. Therefore, it is not possible to say that different doses of mifepristone or routes of administration of misoprostol are more dangerous than others. However, one can say that abortion-related mortality (whether surgical, medical, or spontaneous) is lower than mortality risk in continuing the pregnancy, or other common risks. Furthermore, it is clear that in terms of all-cause mortality among young women, abortion-related deaths are not a major contributor.

Interestingly, deaths associated with miscarriage appear to be, similar to deaths associated with medical abortion, primarily related to infection.[10] Similar to deaths related to medical abortion, 2 recent deaths from miscarriage have been reported to be related to *C sordellii*.[7] Thus, medical abortion and spontaneous abortion have similar mortality risks and similar etiologies of mortality. This observation is not surprising, given that a medical abortion is simply a medication-induced spontaneous abortion. These similarities point to the pathophysiology of the spontaneous abortion as the common cause—and not to the drugs used to induce the medical abortion.

The Case for Medical Abortion

Reductions in the availability of abortion procedures, whether medical or surgical, would be predicted to increase mortality. In many areas of the United States, access to a medical abortion is greater than access to surgical abortion. For surgical abortion, mortality rates increase by 38% for each additional week of gestation.[7] Thus, if medical abortion were less available, a medical abortion at 8 weeks' gestation may be replaced by a surgical abortion at 10 or 12 weeks, with a much higher mortality rate than an earlier surgical abortion or medical abortion. Additionally, unwanted pregnancies continued to term carry an even higher risk of maternal mortality and are at higher risk for complications, such as very low birth weight.[14]

One or both of the 2 drugs administered for medical abortion have been proposed as the cause of the deaths. Although some may believe that vaginal administration of misoprostol is the cause of infectious deaths in the United States, no evidence exists to suggest that oral administration is safer. Currently, more than half of medical abortions in Europe use vaginal misoprostol. Given that the absolute numbers of medical abortion performed in Europe far exceed those in the United States, we would expect more deaths in Europe if the vaginal misoprostol were the cause. To date, no deaths have been reported in Europe. Additionally, vaginal misoprostol is well studied and routinely used for labor induction and second-trimester abortion in the United States and in most of Europe, without any reports of serious infection with similar organisms. Typically, with these indications, the provider inserts the misoprostol, but no evidence exists to suggest that provider insertion carries a lower risk of infection. Others have proposed that immunologic changes resulting from mifepristone's antiglucocorticoid action may result in death. However, for many years 600 mg (3 times more than what is currently used by most providers) was the standard dose of mifepristone used in Europe and Asia, and no deaths were reported. Further research is warranted to examine the immunologic changes related to mifepristone in early pregnancy.

At the current time, the best strategy to decrease the mortality risk of medical abortion in the United States is unclear. It is important that measures are not taken simply for the sake of action, when it is not clear that the measures will increase safety for women. We think that the causes of mortality in these cases are more likely to be social and policy related than medical in nature. When it became apparent that toxic shock syndrome could be caused by prolonged use of tampons, the US FDA did not remove all tampons from the market; rather, relevant studies were conducted to understand why infections occurred. In this case, a simple behavioral intervention remediated the problem.

Another instructive example is the Dalkon Shield. The Dalkon Shield was an intrauterine device used in the 1970s that was found to be associated with septic abortion in the United States. Lawsuits related to deaths from septic abortion led to the bankruptcy of its manufacturer, A.H. Robbins. Surprisingly, after much investigation resulting from concern over deaths in the United States, the Dalkon

Shield was found not to cause infection or death in Great Britain.[15] Because the device used in the United States was exactly the same as that used in Great Britain, the most logical conclusion is that nonmedical differences exist between the 2 nations. The most glaring differences are overall greater access to healthcare in the socialized system in Great Britain and the inclusion of reproductive healthcare into the overall healthcare system in Great Britain. Research should be performed to determine what social factors, behavioral factors, and policies may be related to increased mortality risk and what interventions may be effective in reducing mortality.

Provision of antibiotics to all women undergoing medical abortion has been proposed. Overall, infection occurs in less than 1 of 200 women undergoing medical abortion with prophylactic antibiotics. To prevent infection with the anaerobe *C sordellii*, a nitro-imidazole (eg, metronidazole or tinidazole) probably would be the best option, but prophylaxis for *C sordellii* has not been studied and treatment after diagnosis of the infection has not been successful.[1] However, the lowest number-needed-to-treat would be 100 000 if antibiotics were 100% effective in preventing all deaths related to medical abortion. It is quite likely that treating this many women with antibiotics would cause a substantial number of adverse events, possibly including anaphylactic deaths.

We feel that maintaining use and availability of the most effective options for medical abortion are important for women who are choosing early abortion. Banning use of vaginal misoprostol for abortion, miscarriage treatment, or labor induction will not be beneficial at the current time. Without more details about the cases of the women who died and more research into the prevalence, diagnosis, prevention, and treatment of *C sordellii*, we cannot begin to provide any evidence-based suggestions for altering care. On the other hand, the potential to increase mortality from misguided interventions is real. We think that the most important relevant policy positions should be to:

- Ensure that all women interested in medical abortion receive appropriate counseling regarding the risk of serious infection and death.
- Ensure that patients have a clear plan for how and who to contact if help is needed. Concealment of the abortion by patients and inability to obtain help early may be a major contributing factor to complications.
- Increase government funding for surveillance and investigation of all serious infections and deaths in pregnant women to better understand associated factors.
- Increase government funding to study the social situations and behavioral patterns of women seeking abortion.
- Provide government funding to investigate the epidemiology of *C sordellii* in pregnant and nonpregnant women.
- Investigate governmental policies in the United States that force abortion care to be separated from routine healthcare. This is one of the most glaring differences between abortion provision in the United States versus Europe and Asia.

Conclusions

The goal of any medical abortion program is to provide safe and effective services for women who choose to terminate a pregnancy in this way. Protecting the health of our patients is our first priority. However, it is important for both the professional and lay communities to recognize that the evidence-based protocols for provision of mifepristone and misoprostol were developed through rigorous scientific studies and, despite tragedy, we need an equally thorough understanding of the causes of abortion-related death before a single drug, regimen, or protocol is held responsible and deemed inappropriate in this setting.

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