Abortion drug's off-label use may have led to deaths

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Preliminary U-M studies indicate that oral use of RU-486's companion drug misoprostol is safe, but vaginal use may undermine body's immune responses. The off-label use of a drug given with RU-486 to terminate a pregnancy may be responsible for a handful of rare, fatal infections seen in women taking the drugs since 2000, a study by University of Michigan scientists suggests.

The drug misoprostol is FDA-approved to be taken by mouth along with RU-486 to end a pregnancy. But many women have received the drug vaginally as part of the two-drug combination, a method of delivery not evaluated by the FDA.

In animal and cell culture studies, the U-M researchers found that misoprostol, when given directly in the reproductive tract, suppresses key immune responses and can allow a normally non-threatening bacterium, *Clostridium sordellii*, to gain the upper hand and cause deadly infection. When absorbed through the stomach, however, the drug did not compromise immune defenses or cause illness.

The study, which appears today online ahead of print in the *Journal of Immunology*, also has implications for understanding dangerous infections that occur during pregnancy.

"Infections after medication abortions are rare, and Clostridium infections after abortion are exceedingly rare," says David Aronoff, M.D., an infectious disease specialist who led the U-M study.

The results provide evidence why doctors should avoid giving misoprostol vaginally and underscore the wisdom of giving it by mouth instead, says Aronoff, an assistant professor in the Department of Internal Medicine at the U-M Medical School. "The findings should help make a safe procedure even safer."

Context: More than a half-million women in the United States have undergone medication abortions safely using the two drugs since the FDA approved the method in 2000.

The new study suggests that Planned Parenthood decided wisely when it issued a warning in 2006 that advised doctors against off-label vaginal use of misoprostol in medication abortions. But many clinicians and patients have opted to use misoprostol vaginally instead, in part to avoid side effects women often have when receiving the drug by mouth.

Out of the hundreds of thousands of women who have taken the two-drug combination safely, there have been eight reported deaths after infections of Clostridium bacteria. The drug was given vaginally in all but one of these cases. Six out the eight women were infected with Clostridium sordellii, a type which rarely causes illness in people. The other two contracted a related Clostridium bacterium.

Clostridium sordellii is being closely watched by the federal Centers for Disease Control and Prevention and others because of the abortion-related deaths and because it is biologically very similar to another form of Clostridium bacteria, Clostridium difficile. C. difficile is of great concern especially in hospitals and other clinical settings, where it is causing increasing rates of infections.

Study findings: The U-M scientists showed that rats given misoprostol injected in the uterus and then exposed to Clostridium sordellii had high mortality rates: 80 percent died within four days. By contrast, rats given

misoprostol through the stomach and exposed to the bacteria showed no increased mortality over infected animals that did not receive the drug.

Cell culture studies also revealed misoprostol weakened several key immune defenses in the reproductive tract. The drug suppressed the action of macrophages, immune cells that normally engulf and kill invading bacteria, and the action of neutrophils. It also inhibited certain other immune defenses, including the production of anti-bacterial chemicals normally made by cells lining the uterus.

Implications: The study results have implications for a much wider segment of women who experience several kinds of infections, including bacterial, viral and parasitic infections that can threaten a healthy pregnancy. Among these are group B Streptococcus, rubella and toxoplasmosis infections.

Infections during pregnancy are cause for great concern, because they are thought to contribute to pre-term births, stillbirths and birth defects. Worldwide, nearly seven million women develop infections during or after childbirth, resulting in one million premature births, stillbirths and maternal deaths. Preterm births are a growing problem.

Misoprostol is actually a synthetic version of one of the body's own suppressors of the immune response, called prostaglandin E2 (PGE2). Natural suppressors help keep a fine balance between an active or overactive immune response.

PGE2 and other prostaglandins, bountiful in the reproductive tract during pregnancy, are thought to help keep a woman's immune system from attacking the fetus as foreign. But it's possible that the high levels may also leave women and their developing fetuses more vulnerable to certain microbes.

"From this research, we are learning about how PGE2 regulates reproductive-tract immunity. Because prostaglandins are made in abundance in the pregnant uterus and have already been implicated in infections, we are increasingly realizing their potent immune regulatory actions," Aronoff says.

"Since infections are a great cause of illness and death in pregnancy, this seems to be a very ripe area to study in efforts to develop better preventive and therapeutic strategies against the complications of pregnancy."

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