Comment on "Misoprostol Impairs Female Reproductive Tract Innate Immunity against Clostridium sordellii"

Caitlin Shannon and Beverly Winikoff

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Letters to the Editor

Comment on “Misoprostol Impairs Female Reproductive Tract Innate Immunity against Clostridium sordellii”

We read with interest the recent article by Aronoff et al. published in The Journal of Immunology (1). The authors present data on the relationship between misoprostol exposure and the suppression of innate immunity in the rat. However, for the many reasons detailed below, we disagree strongly with their extrapolations to the effect of vaginal use of misoprostol for pregnancy termination in women.

First, in this study misoprostol was not administered vaginally but via intraterine injection. We know of no study indicating that the local immune response of uterine tissue to direct misoprostol application is similar to what occurs following vaginal administration. Additionally, we have no data that allow us to conclude that vaginal administration would result in higher endometrial concentrations of misoprostol than would occur following other routes of administration.

Second, the bacteria were introduced via the uterus and the uterine horn was subsequently tied off, a model that does not mimic the presumed nature of pelvic infection with Clostridium sordellii among women.

Third, the dose given to rats was nearly 20 times the standard dose used for pregnancy termination. In addition, the previously demonstrated immune response to misoprostol in humans given misoprostol orally lasted 8–10 h (2). Yet, among the reports of C. sordellii infections among women, women presented with symptoms 3–5 days following misoprostol exposure.

Fourth, caution is warranted when applying results from nonhuman research to humans (3). Moreover, the rats were not pregnant, an immune state markedly different from pregnancy.

Finally, there is no evidence that vaginal misoprostol use in women is uniquely responsible for the fatal toxic shock associated with medical abortion. A case was recently reported following nonvaginal misoprostol administration (4). The estimated relative risk among women taking misoprostol vaginally and nonvaginally in the United States is nearly identical. In other countries, where vaginal misoprostol use is the standard of care for medical abortion, hundreds of thousands of women have used misoprostol vaginally without a single reported infection.

The potential for misconstruction and misuse highlights the important duty that scientists have in explaining and interpreting research so that advocates and media can report on them responsibly.

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References

Response to Comment on “Misoprostol Impairs Female Reproductive Tract Innate Immunity against Clostridium sordellii”

We thank Shannon and Winikoff for their interest in our work and their thoughtful comments. We examined the effects of misoprostol on intrauterine infection but not the influence of this agent on early events such as colonization of the vagina or ascension into the uterus by Clostridium sordellii (1). While the rapidly lethal death caused by intrauterine C. sordellii infection in rats mimics clinical aspects of human pelvic infection, we agree that an alternative model is necessary to explore misoprostol’s effects on colonization and initiation of infection. Whether effects of misoprostol on vaginal innate immunity parallel effects observed in the uterus awaits investigation.

While immunosuppressive effects in humans given a single dose of oral misoprostol last for hours (2), women suffering from postabortion C. sordellii toxic shock syndrome presented several days following vaginal misoprostol exposure. These findings are not contradictory. Vaginal misoprostol behaves pharmacologically different from oral misoprostol, with greater systemic exposure when it is given vaginally (3). It is possible that uterine contamination with relatively few C. sordellii bacteria is temporally related to vaginal misoprostol application. Acute suppression of innate immune defenses against these few clostridia might allow infection to be established, only to become overtly symptomatic days later as the bacterial load increases. The clinical pharmacology of vaginally applied misoprostol requires further study. Although we speculate that uterine misoprostol concentrations are greater with vaginal application, this has not been assessed.

Shannon and Winikoff raise a key point about dosing misoprostol in the rat model. While the absolute dose of misoprostol given to rats (10–90 µg) was lower than that used in women (400–800 µg), rats received greater doses on a per kilogram basis (75–600 µg/kg) than humans receive (~5–10 µg/kg).
Rat misoprostol doses were based on studies defining the effective concentrations for abortion in this species (4). Therefore, doses of misoprostol used in rats were comparably efficacious to human doses. This caveat of animal research limits the generalizability of our findings to humans. We agree that the use of nonpregnant animals was a limitation. Future studies are needed to examine the immunological properties of misoprostol in the context of pregnancy or its loss.

There is a lack of evidence showing that vaginal misoprostol use in women is uniquely responsible for the fatal toxic shock associated with medical abortion. If vaginal misoprostol use is a causal determinant of risk in postabortion C. sordellii toxic shock, it is likely one of many factors still uncharacterized. Clostridial endometritis occurs in the absence of intravaginal misoprostol use, although epidemiological data clearly associate postabortion infection with this practice (5–7).

C. sordellii infection complicates <1 per 100,000 medication abortions (8). Studies examining infectious complications of misoprostol were not powered to detect the occurrence of this rare infection, let alone study risk factors. Although our data do not provide direct evidence that intravaginal misoprostol is a causal risk factor in human C. sordellii infections, they provide the foundation and rationale for conducting more investigations to examine the important points raised by Shannon and Winikoff.

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