Probing prostaglandins and pregnancy

Each year, infections and inflammations can be more than just a minor nuisance for millions of pregnant women. They can cause dangerous problems before and during birth, and can contribute to birth defects in ways that aren’t well understood.

At the same time, for a very small number of healthy women who sought to end a pregnancy with the drug combination of RU-486 (a progesterone receptor blocker) and misoprostol (a synthetic prostaglandin), infections have proven deadly. Though it has only been reported a handful of times, the phenomenon has led to changes in the way medical abortions are performed.

Is there a common thread between these two very different situations? The answer may be yes.

David Aronoff, MD (right), is trying to find that thread, and unravel mysteries about the role of infection in the female reproductive tract. As a U-M infectious disease specialist with training in clinical pharmacology and immunology, he is investigating the role of a molecule called prostaglandin E2 (or PGE2) and its synthetic version, misoprostol, in the susceptibility of women to bacterial infections of the uterus. This includes the deadly infections that followed medical termination of pregnancy in some women, and the broader issue of pregnancy complications and birth defects.

This past year, he received new funding for this work through three prestigious grants awards in national competitions. Now, with funding from the National Institutes of Health, the Doris Duke Clinical Scientist Development Award Program, and the Early Career Development Award from the Central Society for Clinical Research, his laboratory team is hard at work to find out what role PGE2 plays, and how its action might be altered.

Prostaglandin E2 is one of a group of lipid molecules that the body makes as part of the immune response to infection or injury. Although PGE2 promotes inflammation by bringing about the hallmark signs of inflammation (warmth, redness, and swelling) at sites of infected or injured tissue, it also appears to suppress immunity by triggering a cascade of signals to immune-response cells called macrophages, neutrophils, and epithelial cells.

For several years, Dr. Aronoff worked with Marc Peters-Golden, MD, of the Pulmonary & Critical Care division of the department, probing the role of PGE2 in lung and respiratory tract inflammation, especially its role in suppressing immune responses and potentially increasing the risk of infection.
But then, a federal Centers for Disease Control & Prevention report on the deaths of women taking RU-486 and misoprostol caught Aronoff’s attention. The sudden deaths resulted from uterine infections by bacteria that rarely cause human disease, namely *Clostridium sordellii*—so it seemed possible that something about the drugs used in the medical abortion procedure could have allowed the infection to develop or rage out of control.

And although the deaths occurred in just a handful of women among the millions who have used RU-486 and misoprostol to end a pregnancy, the situation was grave enough to warrant a warning from the CDC, to encourage vigilance by physicians who were providing medical abortions.

Aronoff knew that misoprostol, one of the two drugs used in the RU-486-based regimen, mimics the activity of PGE2. He also noted that most of the women who had died of massive *C. sordellii* infections after taking RU-486 had administered the misoprostol vaginally, at a much higher dose than what would be taken by mouth. One woman who died had taken a double dose orally. Could this combination of high dosage and, in most cases, direct contact with the reproductive tract be the key to the women’s vulnerability?

In a presentation at the national 2007 Reproductive Health Conference, Aronoff and his colleagues presented data from animal cell-culture studies, showing that misoprostol did indeed inhibit the ability of macrophages and neutrophils in rats to fight off infection.

Now, in research being performed in collaboration with Lisa Harris, MD, PhD, of the U-M Department of Obstetrics & Gynecology, Aronoff is studying the PGE2/misoprostol link further. The research is uses human uterine lining tissue obtained from surgical abortion patients, allowing the team to study directly how RU-486 and misoprostol affect the protective immune barrier between a woman’s reproductive tract and the rest of her body.

As Aronoff and his team explore the impact of misoprostol on the immune-response capability of the human female reproductive tract, they also hope to discover new insights into the much broader issue of how infections occur in that organ system, and how they can affect a pregnancy as it proceeds toward delivery.

As her pregnancy progresses, a woman’s body makes an abundant amount of PGE2, which is likely to influence how her body responds to infectious agents.

At the same time, research has shown that some of the most common complications of pregnancy in both the Western and developing world are due to infection. Some estimates suggest that half of all premature births are related to infection.

By studying how the female reproductive tract responds to infectious agents, and what factors alter that response, Aronoff and his team hope to uncover ways to improve the safety of pregnant women, whether they’re choosing to end a pregnancy or carry it to term.

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**Clostridium difficile**

Most vegetative cells are killed in the stomach, but spores can survive the acid environment.

C. difficile spores germinate in the small bowel upon exposure to bile acids.

Right: *C. difficile* vegetative cells produce toxins A and B and hydrolytic enzymes

1. Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment

2. Opening of epithelial cell junctions

3. And epithelial cell apoptosis

4. Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation

5. And watery diarrhea

“Clostridium difficile-associated diarrhea in adults” — Reprinted from, CMAJ 6-Jul-04; 171(1), Page(s) 51-58 by permission of the publisher. © 2004 Canadian Medical Association
Exploring the microbiome—the molecular way

Every human being is a walking, talking, breathing, eating zoo.

Inside our bodies, and especially inside our digestive tracts, billions of bacteria, viruses, and fungi make their homes without any harm to us. In fact, without them, we’d be miserable.

This jungle of microbes helps us digest our food, get rid of our waste, and fight off microscopic invaders. We’ve evolved to need them, just as they’ve evolved to need us. But we don’t understand them all that well—and we surely don’t comprehend what happens when something happens to disturb them.

All that may change in the next few years, as the federal government pours millions of dollars into understanding this “microbiome” that rivals the Amazon rain forest in complexity and importance. The Human Microbiome Project, launched in late 2007, seeks to understand how microorganisms interact with our bodies and with one another in both healthy and diseased states, and to use modern DNA tools to study microbes that may have eluded researchers to date.

But even before that project was announced, one U-M Infectious Disease faculty member was already hard at work on these kinds of questions and techniques. Vincent Young, MD, PhD (above), was recruited from Michigan State University to lead a laboratory team that is tackling important issues in microbiome biology, using tools and tactics adapted from other fields and applying them to human disease.

One of the team’s interests is the colonization of the human gut by the bacterium Clostridium difficile (C. difficile), a notorious bug that earned its “difficult” name by being especially hard to grow in culture. C. difficile is the bane of millions of people each year, causing diarrhea among many who take antibiotics to quell an infection. In one-quarter of patients, C. difficile-associated diarrhea (CDAD) comes back again and again, while most others get over their initial bout quickly. And for older and weaker people, especially those in hospitals and nursing homes, an episode of CDAD can keep them laid low much longer—or even prove deadly.

To find out what’s going on in the guts of people with CDAD, Dr. Young and his MSU colleagues used techniques that allow them to find tiny fragments of ribosomal RNA in patient samples. They then determine which RNA belongs to which kind of bacteria.

In a paper published in early 2008 in the Journal of Infectious Diseases, they reported that patients with recurring bouts of CDAD had far less diverse populations of microorganisms in their guts, compared with patients who had improved after a single episode of CDAD, and those who had not had CDAD at all.

As he continues his work at U-M, Dr. Young and his team are continuing to apply these molecular genetic techniques to look at the ecology of the human gut. Working with Gary Huffnagle, PhD, of Microbiology & Immunology, and the Pulmonary & Critical Care division, they are looking for clues as to how disturbances in the human microbiome are linked to inflammatory bowel diseases (IBDs) such as colitis and Crohn’s disease.

One tool that’s useful in this search is a strain of mouse that has a disease similar to human IBD, and lacks the gene for an immune system component known as interleukin 10. By looking at how these mice respond to different infectious agents, and to a bacterial factor known as Cytolethal distending toxin, they hope to understand how the gut’s flora and fauna respond to insults—and which treatments might help them bounce back.

As the research continues, Dr. Young looks forward to having access to samples from the large pool of U-M patients with gastrointestinal diseases, both chronic and acute. A high-throughput DNA sequencing core will accelerate his work even further, allowing him to study the zoo inside each of us.