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## Preventing Newborn Infections: Is a New Approach in Order?

What happens when a strategy seems like it's working? With the advent in 1996 of the standard practice of giving at-risk women pre-delivery antibiotics, and with the protocol being refined in 2002, the occurrence of disease due to group B streptococcus (GBS) in newborns has been dramatically reduced. Similarly, the number and severity of Cesarean section infections in delivering mothers have also been greatly lowered. These remain, of course, remarkably positive achievements, borne out and documented by copiously gathered data.

**William J. Ledger, MD**, former Obstetrician and Gynecologist-in-Chief, New York Presbyterian/Weill Cornell Medical Center, was one of the first people to author a paper on antibiotic prophylaxis in gynecology. "I was very excited about it because we'd demonstrated that the infection rate was really much less when we used antibiotics in certain groups of patients," says Dr. Ledger, a noted pioneer in the diagnosis and treatment of gynecologic infections and the founder and first President of the



Dr. William J. Ledger

Infectious Diseases Society for Obstetrics and Gynecology. "But there is much more to find out about the efficacy of this regimen in the long-term."

Dr. Ledger, though one the protocol's research forerunners, is also among its most ardent, and curious, critics. "There is no question that this

*(continued on page 2)*

## Pursuing Multiple Perspectives on Premature Cervical Remodeling

One in eight pregnancies in the United States results in a premature birth, accounting for approximately 500,000 such births each year – a number that drew the attention of **Joy Vink, MD**, during her residency and fellowship training in Obstetrics and Gynecology. "The high rate of premature birth really struck me," says Dr. Vink, a Maternal-Fetal Medicine specialist in the Department of Obstetrics and Gynecology at New York Presbyterian/Columbia University Medical Center. "Even though there are a lot of women who deliver at 36 weeks, there is a large number who also deliver extremely prematurely at the cusp of viability –

25 and 24 weeks. In many of these patients, the cervix undergoes remodeling, softens, and dilates resulting in preterm birth."

Traditionally referred to as cervical insufficiency, the condition is now termed premature cervical shortening or premature cervical remodeling. The clinical definition of cervical insufficiency can vary, says Dr. Vink, yet the pathophysiology of spontaneous preterm birth remains largely unknown. Regardless of the inciting event, the end result in all cases of preterm birth is premature cervical remodeling followed by cervical

*(continued on page 3)*

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— Dr. Joy Vink

## Preventing Newborn Infections: Is a New Approach in Order? (continued from page 1)

strategy has lowered the risk of having a group B streptococcus infection in a newborn, as well as the incidence of post-surgical Cesarean infections,” says Dr. Ledger, acknowledging the broad and affirmative outcomes, while also questioning a regimen that seems to be working. “It is not that we suddenly have a bunch of infections that we can’t treat. The problem, however, is with the monitoring that we are doing. We are looking at immediate results, not long-term results. We are not sufficiently probing the data for its clinical significance, and we are not sensitively monitoring the effects produced by the use of so many antibiotics in the long-term, and for so many.”

Dr. Ledger and his colleagues question the efficacy of evidence-based medicine, which emphasizes statistical rather than clinical significance. “The antibiotics that we call into play to treat mothers in labor are specifically employed if they are culture-positive for group B streptococcus,” Dr. Ledger says. “And we do that to try to cut down the risk of the newborn developing an infection with the GBS.”

But Dr. Ledger is suggesting that the answers are more various and more specific. “If you look at one subpopulation, for example, very premature babies in the weight range of 500-1,500 grams, there has been a reduction in group B strep infections in that population, but an increase in infections due to *E. coli*, which is an organism not covered by the group B prophylaxis regimen,” he says. “So if you look in that specific population of premature babies, the actual rate of newborn infections has been unchanged. Evidence-based medicine needs a critical eye so that studies are not including a number of patients with different risk factors under the same umbrella.”

In a 2013 commentary published in the *British Journal of Obstetrics and Gynecology*, Dr. Ledger and his co-author Dr. Martin Blaser reported that 20 to 40 percent of women in labor are receiving antibiotics before they deliver. The baby, of course, receives each of the antibiotics given to the mother. This regimen is, at least in part, in response to statistics that clearly demonstrate that women delivering by Cesarean section are at far greater risk of infection than women giving birth vaginally. “But it is very patterned, very clearly patterned,” Dr. Ledger suggests. “For a woman who has been in labor for six hours, has membranes ruptured, and now requires a Cesarean delivery, there is a very high rate of infection. But for the woman having an elective Cesarean delivery, who is not in labor, her risk of infection is very low. Should we be giving all these antibiotics to all these mothers and also to all these children – where there is an impact – to prevent a small number of infections?”

### Questioning Long-Term Effects, Reconsidering Protocols

Are these antibiotics, given indirectly to so many infants so early in their lives, producing serious negative effects? Research suggests that changes in the composition of the indigenous microbiota of newborns have the potential to influence childhood development and disease risk. These changes in the aboriginal gastric microbial makeup in early life can have profound and serious consequences later in life. In one example, when *Helicobacter pylori* disappeared from the gastric microbiota of mice, the result was a decrease in gastric T-cell population. Such a change could be responsible for increases seen in childhood asthma, allergic rhinitis, and skin allergies. The absence of *H. pylori*-mediated regulation of gastric adipokines, such as ghrelin and leptin, at a time when adiposity is being programmed, could contribute to the growing number of obese children and adults.

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According to the CDC, the number of people with asthma grew by 4.3 million between 2001 and 2009. In that same timeframe, asthma rates increased most among African-American children, an almost 50 percent increase. The economic and human cost of treating such increases in serious and prolonged illnesses is profound and growing. More than one in six children ages 6 to 19 are considered obese. While the etiology of these changes could be from several sources, Dr. Ledger argues that we can use research to find more refined and specific regimens that treat women at risk for infection during childbirth in a far safer and more individualized approach.

“There are markers that look at risk factors for women undergoing Cesarean sections,” says Dr. Ledger. “Before any guidelines were established, there were 5.9 cases of GBS sepsis per 1,000 births in the highest risk premature infants. To protect one small baby from infection, 100 others were exposed to antibiotic treatment. There are now delineated risk factors.”

The incidence of GBS infection in the newborn is greater for women who have previously delivered an infant with GBS infection and those who have GBS bacterium in the first trimester, and in premature deliveries, before 37 weeks. Prolonged delivery, more than 18 hours, with ruptured membranes, is also a marker associated with increased risk of GBS infection. Women who choose elective Cesarean delivery, whether or not there is the presence of GBS in the vaginal or intestinal tracts, are at very low risk for giving birth to an infected infant.

“When I began my career in academic medicine so little was known about women and infections,” says Dr. Ledger. “One of the things that intrigued me is that most of the writing in the textbooks did not match what we were seeing clinically. They kept talking about ‘sterile abscesses,’ which made no sense. There was no understanding of anaerobic bacteria. We were serving 13,000 women a year, so there were ample opportunities for clinical studies.”

Dr. Ledger underscores the importance of continued research based on clinical evidence and long-term follow-up so that safe protocols can be designed that respond more individually and responsibly. “We can choose statistically that we will treat 100 women and prevent one or two infections, and that is statistically significant when you major in large numbers of patients,” states Dr. Ledger. “But is it right?”

#### Reference Article

Ledger WJ, Blaser MJ. Are we using too many antibiotics during pregnancy? A commentary. *British Journal of Gynecology*. 2013 Nov;120(12):1450-52.

#### For More Information

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## Pursuing Multiple Perspectives on Premature Cervical Remodeling *(continued from page 1)*

dilation and delivery of the fetus. Many premature babies do not survive, and many who do face lifelong disabilities and chronic illnesses.

“We don’t know what causes premature cervical remodeling,” says Dr. Vink, who began research in this area during her residency in OB/Gyn at Georgetown University, where she frequently treated patients struggling to prevent preterm birth. She continued her research into the causes and prevention of preterm birth during her fellowship in Maternal-Fetal Medicine at NewYork-Presbyterian/Columbia. In 2012, she was awarded the Society of Maternal Fetal Medicine/American Association of Obstetricians & Gynecologists Foundation Scholarship that provided support for her translational research on the biochemical and biomechanical etiologies of cervical insufficiency/preterm cervical shortening and preterm birth. And this year, Dr. Vink was one of four young physician-scientists to be named a Louis V. Gerstner, Jr., Scholar at Columbia, which will continue to fund her research in this area.

Dr. Vink’s research goal is to delineate the biochemical pathways involved in premature cervical remodeling and, once established, to translate this knowledge to rational, noninvasive, and easily adaptable approaches to measure cervical remodeling biomarkers. These biomarkers would identify women at risk for preterm birth earlier in their pregnancy and provide an opportunity for interventions such as steroids for fetal lung maturity or transport to a hospital capable of managing preterm deliveries.

“Part of the problem is that there is not a lot of basic science being conducted within this particular field of premature cervical remodeling,” says Dr. Vink. At Columbia, Dr. Vink began to look at matrix remodeling as a possible cause. “The cervix is mostly collagen and the strength of the collagen is what we thought keeps the cervix together,” says Dr. Vink. “We believed that for whatever reason there is inherent weakness in that collagen structure, but what triggers that remodeling process so that it becomes weaker is unclear. There are theories that it might be inflammation-based or bacteria-based.”

### Understanding the Dynamics of Pregnancy

As Dr. Vink explains, pregnancy is a dynamic process in which not only cells and chemicals are changed, but also mechanical properties. “There are mechanical forces that are exerted on the cervix when the cervix is stretched as the pregnancy grows and when the uterus contracts,” she says. “In the past, people have studied problems like this from a biological or a physiological perspective, but nobody has taken a multidisciplinary approach to figure this out – one that would entail basic scientists, clinicians, systems biologists, and mechanical engineers. We must attack it from multiple perspectives – biochemical, biological, and mechanical – and that is what we are doing here at Columbia.”



*Dr. Joy Vink*

Dr. Vink and her Columbia colleagues, a multidisciplinary group of young physicians and engineers, are taking another look at the cervix. “Nobody has really looked at the architecture of the cervix since the 1940s,” says Dr. Vink. “All of the landmark studies have said that it is mostly collagen or that there are very few cells there. That was research done back then and no one has repeated it since.”

In trying to determine how tissue responds to mechanical forces, says Dr. Vink, we need to first examine and understand the overall structure of the tissue, such as the collagen network and cellular makeup, and then apply certain mechanical forces to see how the tissue responds to that force. “Scientists have always thought the uterus was mostly muscle and the cervix was this homogenous collagenous structure attached to the bottom of the uterus

passively remodeled, dilated, and shortened as the uterus contracted. We found that there is a lot more smooth muscle in the cervix – just as in the uterus. That gradient of smooth muscle cells would change from the top of the cervix where it meets the uterus, and down toward the outside of the vagina.”

This knowledge generated additional areas of inquiry for Dr. Vink and her colleagues: What is the role of the smooth muscle cells in the cervix? Are they there to keep the cervix closed? Do the mechanical forces on the uterus stretch those cells and cause the collagen to start to weaken by secreting enzymes and proteins?

Dr. Vink recently identified a receptor (ANTXR2) in the human cervix that may act as a “stretch-sensor” as the pregnancy grows and may control the subsequent cervical remodeling process. Her goal is to learn how the human cervix naturally responds to stretch, how the cervix from a woman with premature cervical remodeling responds, and whether the ANTXR2 receptor is involved. The research should determine if the receptor could be targeted to prevent premature cervical remodeling and preterm birth.

Dr. Vink anticipates that their research will eventually lead to the development of an effective, personalized diagnostic tool. Currently, **Kristin Myers, PhD**, one of Dr. Vink’s collaborators and an engineer at Columbia University, is building anatomically correct computer simulation models of the pregnant abdomen. “These personalized computer models are innovative because we can input the mechanical and biochemical properties of a woman’s cervical tissue into these computer models and then simulate or predict how that woman’s cervix will function in pregnancy,” explains Dr. Vink. “These computer models will also help us understand how current therapies, such as a cerclage or pessary, work or don’t work on certain patients.

“Down the road we hope to come up with new targets that we can attack with medications or different solutions that would

*(continued on page 4)*

## Advances in Gynecology

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### Pursuing Multiple Perspectives on Premature Cervical Remodeling (continued from page 3)

actually enhance cervical strength,” adds Dr. Vink. “All we can do for treating a weak cervix right now is to give a woman progesterone and place a cervical cerclage or a pessary – and these therapies fail in a good percentage of women. In order to discover new, more effective therapies, we first need to better understand how a cervix remodels in a normal pregnancy. Only then can we start looking at how that normal process goes awry when the cervix remodels prematurely leading to preterm birth.”

In a recent study, Dr. Vink and her colleagues in the Department of Obstetrics and Gynecology at Columbia looked at the rate of cervical shortening after cerclage placement and its association with the risk of spontaneous preterm birth. “We found that the rate of cervical shortening among patients with cerclage who deliver at term is slower than that of those who deliver preterm,” says Dr. Vink. Their findings suggest that monitoring cervical length after cerclage placement via sonogram with particular attention to the rate of cervical shortening may be useful in identifying which patients are at highest risk.

#### Preterm Birth Prevention Center

In addition to Columbia’s robust research program in the field of preterm birth, plans are currently underway to create a Preterm Birth Prevention Center. “The goal of this center of excellence is to decrease the rate of spontaneous preterm birth by implementing standardized best clinical practice and performing cutting-edge research to better understand the complex pathways that lead to

preterm birth,” says Dr. Vink. “Nationwide, there are only a handful of centers of excellence in preterm birth; and of the few that exist, the majority are focused solely on research. The Preterm Birth Prevention Center at NewYork-Presbyterian/Columbia will be the only center in the Northeast that incorporates providing both specialized patient care to women at risk for preterm birth and access to the latest research.”

Clinically, the Preterm Birth Prevention Center will provide a “one-stop shop” experience for patients at risk of spontaneous preterm birth. This includes women with the following risk factors: a history of sPTB, multiple gestations, a short cervix, extremes of BMI, smoking, bleeding, and African-American race. Specifically, the Maternal-Fetal Medicine providers in the Preterm Birth Prevention Center will provide expert consultative services to establish a specialized management plan for the patient. In terms of research, the Center will be a centralized location where patients can have access to ongoing and future studies to decrease preterm birth.

#### Reference Article

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#### For More Information

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