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Editorials and Comments

Editorial: Intrauterine Infection and Why Preterm Prevention Programs Have Failed

Preterm birth is the major pregnancy-related problem in the United States, accounting for nearly 75% of the neonatal mortality and as much as 50% of long-term neurological damage in children.[1] Dramatic changes have occurred in survival of both term and preterm infants since the 1960s, mostly due to improvements in neonatal care. As a result, the majority of the residual neonatal mortality now occurs in very preterm infants. Currently, nearly 60% of all neonatal mortality is found in the 1% to 2% of infants born at less than 30 weeks gestational age or weighing less than 1000 g at birth. Unfortunately, there has not been a similar reduction in the rate of preterm birth. In fact, data from multiple sources indicate that the rate of preterm birth actually has been rising since the mid-1980s.[2] Why the rate of preterm birth continues to be excessive and why this rate has increased despite the following remains elusive: increasing availability of prenatal care, the development of comprehensive prenatal care programs, a greater use of pharmacologic agents to inhibit labor, home uterine activity monitoring to detect early preterm labor, and a proliferation of other interventions. However, it is very clear that our current approaches to the prevention of prematurity have failed.[3]

Over the years, several observations regarding spontaneous preterm delivery have loomed so large that any proposed hypothesis (such as the one that will be developed in this editorial) regarding its etiology must offer explanations for these phenomena as well. The first of these phenomena is that Black women have substantially more spontaneous preterm birth than White women and that this disparity increases below 30 weeks' gestation. The second is that women who deliver preterm, especially those who deliver very early, have substantially more histologic evidence of chorioamnion inflammation than women who deliver later.[4] As many as 80% of women delivering prior to 30 weeks have histologic chorioamnionitis. Recent studies indicate that if the membranes and the amniotic fluid are cultured carefully in women delivering spontaneously at less than 30 weeks, bacteria will be found in 60 to 80%.[5,6] Why both inflammation and bacterial colonization are more common in the membranes of these women than in women who deliver at later gestational ages must be explained.

It is well known that women who have one preterm birth tend to repeat that outcome. Less well known is the observation that women who deliver early in the preterm period, i.e. around 24 weeks, are at substantially greater risk for repeating an early preterm birth than women who deliver at or near term.[7] Any hypothesis regarding the etiology of spontaneous preterm birth must account for the repetitive nature of these births. Infants born at early gestational ages have a much greater incidence of neonatal sepsis than infants born later. To date, it has been assumed that the etiology of this increased risk of sepsis is a relatively immature defense mechanism against the organisms encountered in the postpartum period. While this is a plausible explanation, it is important to determine if there are others. For example, these infants may have been exposed to bacteria in utero more frequently than infants born later in gestation.

Also requiring explanation is the fact that immigrant Hispanic women in the southeastern United States and Black Caribbean women on the East Coast have

substantially lower preterm birth rates than women of similar ethnic origins born in the United States. Acculturation appears to be associated with a greater risk of preterm birth despite the fact that it often is associated with an increase in the standard of living. It is important to define which aspects of acculturation are associated with an increased risk of prematurity.

The etiology of preterm birth that follows the spontaneous onset of labor or spontaneous rupture of the fetal membranes has been an enigma for many years. More recently, the relationship between intrauterine infection and spontaneous preterm birth has become better understood.[8,9] Up to 40% of women in spontaneous labor will have bacteria in both the amniotic fluid and the membranes, and an additional 20% will have organisms in the membranes but not in the amniotic fluid. Associated with these microorganisms is an increased production of various proinflammatory cytokines that can be detected in the amniotic fluid and participate, both directly and indirectly, in various pathways leading to the onset of contractions, changes in cervical consistency, and rupture of the membranes.[8,10] In recent years, the bacteria associated with spontaneous delivery have become better characterized, with the more common being *Ureaplasma urealyticum, Mycoplasma hominis, Bacteroides,* and *Gardnerella vaginalis* species.[8,9] These microorganisms are, for the most part, of low virulence and may exist asymptomatically for long durations in the vagina and the uterus.[11]

The most obvious explanation for the difference in Black–White early prematurity rates is different patterns of bacterial colonization. Black women have a substantially higher prevalence of potentially pathogenic organisms than do White, Hispanic, or Asian women.[12] Bacterial vaginosis, defined as an overgrowth of various bacteria in the vagina, is two to three times more common in Black than White women. Because bacterial vaginosis is associated with an odds ratio for spontaneous preterm birth of between 1.5 and 3.0, it is not surprising that Black prematurity rates are substantially higher.[13]

The findings that infection is so prominently related to early spontaneous preterm birth, and that early spontaneous preterm births tend to repeat, are likely explained by the observation that the bacteria may not ascend from the vagina during pregnancy but are present in the uterus prior to the pregnancy. There is ample evidence that women may harbor organisms inside the uterus prior to their pregnancies and that this colonization results in a chronic but asymptomatic endometritis. Korn et. al. recently showed that endometritis is quite common in nonpregnant women with bacterial vaginosis.[14] The intrauterine bacteria included the same microorganisms that are associated with spontaneous preterm delivery.

Evidence is also accumulating that the intrauterine infection that precipitates preterm labor after 20 weeks' gestation is present at least several weeks earlier. As an example, in a report by Cassell et al., amniotic fluid colonization with *Ureaplasma urealyticum* was identified at 16 weeks, but was not followed by spontaneous preterm birth until 24 weeks.[15] Several larger studies have confirmed that, when organisms are present in the amniotic fluid prior to 20 weeks, the pregnancy generally terminates spontaneously within the next 4 to 8 weeks.[10,16] Recently, elevated midtrimester amniotic fluid proinflammatory cytokines, present in asymptomatic women at 16 to 18 weeks' gestation, were found to be predictors of subsequent preterm delivery.[17]

Consider what might happen if the uterus is colonized with bacteria prior to pregnancy. Certainly, conception is not prevented. There also is little evidence that these women abort spontaneously in the first 12 weeks at a rate much higher than do other women; most spontaneous first-trimester abortions are due to a chromosomal etiology. Women who have chronic endometritis, however, may maintain the infection in asymptomatic form until the membranes adhere firmly to the decidual lining at about 20 weeks' gestation. Since the membranes apparently seal the uterus closed at that time, colonizations that have been quiescent may only then become symptomatic.

Unless the infection is cleared by the body's defense mechanisms, production of inflammatory cytokines by the decidua will initiate labor, and the infant will be born preterm. If most of the infection-related preterm births occurred within 4 to 8 weeks after the membranes seal the uterus closed, this would explain why most of the spontaneous preterm births associated with infection occur prior to 30 weeks. This type of infection also would explain why women who have one early spontaneous birth are so prone to have a second, since there is no reason to believe that after the infant delivers, the intrauterine bacterial colonization disappears spontaneously. Additionally, slow resolution of the infection following preterm delivery may explain the phenomenon that repeat preterm birth is more likely when conception occurs soon after a previous preterm birth.

Taken altogether, chronic colonization of the endometrium with low virulence microorganisms, some of which are transmitted sexually, has the potential to explain most of the observations related to early spontaneous preterm birth. It can account for the high early spontaneous preterm birth rate in Black women, the acculturation phenomenon, the repetitive nature of early spontaneous preterm birth, as well as the concentration of neonatal sepsis in very preterm babies.

We hypothesize that bacterial vaginosis serves as a marker for women who have a chronic endometrial infection, yet is of little consequence as long as the uterus is free of organisms. We believe that the underlying disease is chronic colonization of the endometrium and that the symptom of that underlying disease is spontaneous preterm labor. Most strategies to prevent spontaneous preterm birth have been targeted either at treating the symptom of spontaneous preterm labor, or at various psychosocial, behavioral, or nutritional characteristics of the mother statistically associated with, but not causally related to, spontaneous preterm birth. It is not surprising that those strategies have failed.[3]

If we are to achieve a real improvement in pregnancy outcome, treatment strategies that are aimed at the underlying disease seem far more promising. In fact, recently reported randomized antibiotic treatment trials of women at high risk for preterm birth who also had bacterial vaginosis showed substantial reductions in spontaneous preterm births.[18] We hope these results can be extended, and further reductions in preterm birth achieved, as we better understand the relationship between preterm birth and infection. □

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Editorial: Family Planning, Sexually Transmitted Diseases, and the Prevention of AIDS—Divided We Fail?

Sexual activity is a basic, if not obligate, antecedent of sexual transmission of both sperm and microorganisms. These two conjoined consequences have spawned three disjoined services, namely, family planning clinics, clinics for sexually transmitted diseases (in practice, limited to those who are immediately treatable), and a host of ad hoc services purportedly aimed at preventing the sexual transmission of the human immunodeficiency virus (HIV). These typically function independently of one another. Might not a naive observer ask if two or even one of these agencies could comfortably combine these three functions, and, in doing so, gain in efficiency and effectiveness?

Contraception has always been the province of family planning clinics. These, growing under the wing of ardent advocates like Margaret Sanger since the 1920s, developed into agencies outside the mainstream of health and curative services. That independence may well, at different times and places, have secured their survival despite swings in political opposition and the hostility of some religious groups toward pregnancy prevention and spacing. Family planning is a movement as well as a service, focusing almost entirely on its own mission. Admittedly, some movement members have advocated an expanded focus on reproductive health or, even beyond that, on the health of women. The assumption of responsibility for reproductive health, however, would properly require provision for the inclusion of services for men. Among both staff and clientele, men are largely absent in these clinics. Nor are most clinics equipped to serve all the health needs of women.

Diagnosis and treatment of diseases known to be sexually transmitted and treatable are the domain of special clinics, the second class of service. These too are often located in space separated from generic health services, and are generally administered directly by public health departments. Such assignments of place and responsibility, one might think, denotes an emphasis on the primary prevention of these transmissible diseases.

In practice, the focus tends to be on the more immediate matters of effective diagnosis and treatment. Health education and a reaching out into communities are lesser commitments. These activities extend to giving out male condoms and, with varying degrees of emphasis and success, advising patients to urge their contacts to come for treatment. But contact tracing and follow up are generally limited to certain categories of patient and are seldom thorough. Despite their public health status, many clinics thus provide a service that emphasizes the medical model and, at best, secondary prevention. The patient comes with a problem and is treated, then sent on his way. Also, one cannot but observe that, in ironic contrast to the family planning clinics, sexually transmitted disease clinics predominantly serve men. These diseases affect at least as many women as men and cause more serious morbidity in women than in men.

Services that seek the prevention of HIV are the third arm of the trio. On the one hand, like services for family planning, they are a product of a social movement. On the other hand, like the sexually transmitted disease clinics, they often are the creation of public health departments and are seen to be their responsibility. A wide range of agencies—voluntary, nongovernment and government, ad hoc social and religious groups—are involved in the prevention of HIV transmission. What is remarkable, and the occasion for this commentary, is the very small contribution to these efforts made by family planning clinics and the sexually transmitted disease clinics.

The reasons for the disjunction and separateness of these services probably