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Aug. 1, 2003

PERIODONTITIS AND PRETERM BIRTH

Is there a link between periodontal disease and preterm birth?

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Mounting evidence suggests that a chronic oral infection may lead to an immune reaction that either triggers premature parturition or contributes to its onset.

Each year over 400,000 infants are born prematurely as a result of preterm labor, preeclampsia, and other adverse events. In fact preterm birth (less than 37 weeks' gestation) is the leading cause of neonatal mortality in the United States, affecting 11% of all live births. And while preterm birth as a result of preterm labor contributes to approximately two thirds of the cases of prematurity, we still don't fully understand what signals the onset of labor in these women. Both preventive and treatment efforts have been disappointing: The preterm birth rate remains unchanged after 30 years.[1]

We have long realized that maternal infection is a risk factor for adverse pregnancy outcomes, and intrauterine infection and bacterial vaginosis (BV) have both been identified as risks for prematurity. The mechanism by which maternal infection mediates early delivery is unclear, but likely involve both maternal and fetal inflammatory and humoral responses. Genetic variation in response to these infections may also play a role in the risk for prematurity.[2]

Clinical infections distant from the uterus, including shigellosis and urinary tract infections, have likewise been associated with preterm

birth.[3,4] Infections more proximate to the reproductive tract, such as BV, trichomoniasis, and Chlamydial cervicitis, seem to increase the risk of preterm birth.[5-8] Intrauterine infection and chorioamnionitis also increase the risk of prematurity.[9, 10]

In the last decade, many investigators have been interested in studying the role of *subclinical* maternal infection in preterm labor. Evidence to support this theory includes the following:

- increased histologic chorioamnionitis in preterm births;
- increased clinical infection after preterm birth;
- a significant association between some lower genital tract organisms and infections and preterm birth or preterm premature rupture of the membranes;
- positive cultures of amniotic fluid or membranes from some patients with preterm labor and preterm birth;
- infection markers seen in preterm birth;
- induction of preterm birth in animal models by bacteria or their products;
- finding in some clinical trials that antibiotics lower the rate of preterm birth or can defer preterm birth.[11]

Finding a correlation between oral infection and prematurity

Exciting new data also suggest that chronic oral infection like periodontal disease may contribute to preeclampsia, preterm birth, fetal growth restriction, and fetal loss.[12-14]

Periodontitis, an oral gram- negative anaerobic infection, is common in women of childbearing age. It presents as infection and inflammation of the gingiva and local support structures of the teeth, resulting in the destruction of the structures supporting the tooth. Fluid that bathes the tooth at the gingival margin, known as gingival crevicular fluid, often contains inflammatory mediators and the oral pathogens associated with periodontitis (Figure 1).

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The mechanisms underlying this destructive process involve both direct tissue damage resulting from plaque bacterial products, and indirect

damage through bacterial induction of the host inflammatory and immune responses.[15] Periodontitis affects up to 50% of the population, including a relatively high proportion of pregnant women.[13,16,17] Advancing age, smoking, and diabetes are some risk factors for the development of periodontitis.[18] While periodontitis is a chronic, local oral infection, there is evidence that both local and systemic inflammation may occur.[15] In addition, periodontitis has recently been recognized as a risk factor for the development of atherosclerosis and rheumatoid arthritis.[19,20]

In 1996, researchers first reported an association between maternal periodontal disease and delivery of a preterm infant. In a case–control study of 124 pregnant women, they observed that women who delivered at less than 37 weeks' gestation or had an infant that weighed less than 2,500 g had significantly worse periodontal disease than control women. The adjusted odds ratio for delivery of a preterm, low-birthweight (LBW) infant was ~7 (i.e., about a sevenfold increased risk) suggesting that periodontal disease may be a previously unrecognized and clinically significant risk factor for delivery of a preterm LBW infant.[21]

Extrapolation from these data suggested that 18% of the preterm, LBW infants born annually might be attributable to periodontal disease, which may thus account for a significant proportion of the $5.5 billion annual hospital costs associated with the care of small babies.

In a subsequent case–control study, independent investigators who looked at 55 pairs of women found that mothers with healthy gingiva were at lower risk for LBW infants.[22] Unfortunately women in both of these case–control studies were examined at the end of pregnancy or after delivery, so there was no way of knowing if the women were exposed beforehand. That means we can't know with certainty if the oral infection actually caused prematurity.

Despite this limitation, these early studies led to the hypothesis that the bacteria that cause periodontal disease (largely gram-negative anaerobes) serve as a source for endotoxin and lipopolysaccharides, which increases local inflammatory mediators. These mediators, including PGE_2, and cytokines, it has been theorized, may contribute to preterm birth.[23]

However a third case–control study, conducted in London, came to a different conclusion. Davenport and colleagues examined 236 infants born at less than 37 weeks' gestation and weighing less than 2,500 g and compared them to a random sample of 507 control infants who were born at 38 weeks' or more gestation and weighing 2,500 g or more.[24] They couldn't find a link between preterm delivery, LBW infants and periodontal disease. Surprisingly, they found that on average, deeper tooth pockets at delivery were associated with a *reduction* in the risk of delivery of a preterm, LBW infant. After they looked at other possible confounding demographic risk factors, the researchers surmised that their findings might have been due at least in part to differences in study

populations.

Trying to determine the mechanism of action

In an effort to better understand the possible mechanism behind the association between periodontitis and preterm delivery, researchers have measured gingival crevicular levels of PGE_2 and IL-1ß in 48 mothers who delivered preterm, LBW infants and compared these levels to those found in control women.[23] They discovered that gingival crevicular fluid levels of PGE_2 were significantly higher in cases, compared to control women. In addition, among primiparous women with preterm, LBW infants, they found a significant inverse association between birthweight and gestational age and gingival crevicular PGE_2 levels.[23]

These investigators also examined maternal and fetal humoral responses to oral pathogens as a possible risk factor or marker for preterm delivery among pregnant women with periodontal disease.[14] There was a 2.9-fold higher prevalence of neonatal IgM seropositivity for one or more oral pathogens among preterm babies, as compared to term babies (19.9% vs. 6.9%, respectively, $P = 0.0015$). A lack of maternal IgG antibody to more pathogenic oral organisms was associated with an increased rate of prematurity, (OR 2.2; 95% CI 1.5–3.8). The highest rate of prematurity (66.7%) was seen in those mothers without any protective IgG response to oral pathogens that delivered an infant who had an IgM response. These data led the authors to conclude that maternal periodontal infection without a protective maternal antibody response is associated with systemic dissemination of oral organisms that may be passed on to the fetus and result in preterm delivery.[14] That in turn led them to create the theoretical scheme outlined in Figure 2.

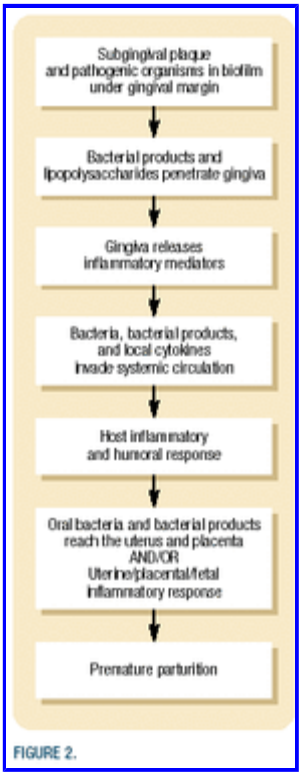

FIGURE 2.

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While the correlation between periodontal disease and preterm birth is exciting—and represents a potentially treatable cause of preterm birth—we still need to interpret the research cautiously. It's possible that maternal periodontal disease may only be a surrogate for another maternal factor that predisposes to preterm birth. Furthermore, while the model presented here is biologically plausible, we still have to determine the underlying mechanism by which periodontal disease may contribute to preterm birth.

Further study on the maternal and fetal inflammatory responses to chronic oral infection and on placental pathology in women with periodontal disease is ongoing to determine the relationship between periodontal disease and preterm birth. And if that research establishes a clear-cut cause-and-effect relationship, we can then offer at-risk patients the appropriate advice on dental hygiene, antibiotics, and dental treatment. In addition, the knowledge gained by these studies will help further the cause for improving the oral health of pregnant women and others.

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Key points

- One case–control study has suggested that periodontal disease may increase the risk of preterm delivery sevenfold.
- Gingival fluid levels of PGE_2—an inflammation mediator—are significantly higher among primiparous women with preterm, LBW infants.
- Mothers who do not have protective IgG and IgM responses to oral pathogens have higher prematurity rates, suggesting that maternal infection, without protective immunity, may cause systemic dissemination of these pathogens, which in turn may be passed on to the fetus.
- If large-scale clinical trials can confirm the link between oral infection and prematurity, ob/gyns can offer at-risk patients appropriate advice on oral hygiene, antibiotics, and dental treatment.

Kim Boggess. Is there a link between periodontal disease and preterm birth? *Contemporary Ob/Gyn* Aug. 1, 2003;48:79-84.