Infection’s Relationship to Prematurity

The United States spends almost 18% of its gross domestic product on health care, yet its infant mortality rate is higher than that in most other developed countries. The latest available data show the United States ranking 29th in the world in infant mortality.

One may ask why the United States continues to have this asymmetry between its investment in health and its health outcome. One way to assess this is to examine the factors that contribute most significantly to infant mortality: prematurity and birth defects. Prematurity remains a vexing problem in the United States – one for which the mechanism and the treatment remain, at best, elusive.

Infection or inflammation is considered to play a dominant role in the pathogenesis of prematurity. Data to support this role have been generated from a number of controlled, uncontrolled, and even laboratory studies. Most recently, additional studies have shown that inflammation or infection occurring within body cavities, including the vagina (bacterial vaginosis) or the oral cavity (periodontal disease) are associated with increased rates of prematurity.

The conundrum that we find ourselves in at this point is that there does not appear to be an effective means of altering the status of infection or inflammation in order to have a direct impact on prematurity. The only way to intervene and improve the perinatal outcome is by a growing understanding of the relationship between infection – most significantly, periodontal infection – and the outcome of prematurity, and the options that can be exercised at this time with regard to oral health, prenatal care, and management pending definitive answers.

We have invited Dr. George A. Macones, an expert in maternal-fetal medicine who has extensively studied the prediction and prevention of prematurity, to serve as our guest author. Dr. Macones is the Mitchell and Elaine Yanow Professor and chair of the department of obstetrics and gynecology at Washington University, St. Louis. In this column, Dr. Macones details the value of counseling our patients about good oral health.

Dr. REESE, who specializes in maternal-fetal medicine, is vice president for medical affairs at the University of Maryland, Baltimore, as well as the John Z. and Akiko K. Bowers Distinguished Professor and dean of its school of medicine. He said he had no conflicts of interest relevant to this column. He is a member of the OB.GYN. News editorial advisory board and the medical editor of this column.

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Periodontal Disease and the Risk of Preterm Birth

During the last 10-15 years, in an effort to improve treating rates of spontaneous preterm delivery and other adverse pregnancy outcomes, investigators have looked at many kinds of clinical and subclinical infections and explored their possible associations to preterm birth.

Bacterial vaginosis is one infection that has been associated in numerous studies with a higher risk of preterm birth. Periodontal disease is another. While not all studies have found an association, there is substantial evidence – mainly from observational and epidemiologic studies – linking periodontal disease to spontaneous preterm birth and identifying the disease as a probable risk factor for preterm delivery.

One of the larger studies was a prospective cohort study involving more than 1,300 pregnant women who were enrolled at 21-24 weeks’ gestation and provided information on various possible risk factors for preterm birth. Later analyses showed that women with moderate to severe periodontal disease were 4.5 times as likely to deliver spontaneously before 37 weeks’ gestation, 5.3 times as likely to deliver before 35 weeks’ gestation, and 7.1 times as likely to deliver before 32 weeks (J. Am. Dent. Assoc. 2001;132:875-80).

Other published studies report lower levels of risk, and a more recent meta-analysis that included 17 studies and more than 7,000 women suggested a 2.8-fold increased risk of preterm birth in women with periodontal disease (Am J. Obstet. Gynecol. 2007;196:135.e1-7).

Today, interestingly, we know that bacterial vaginosis and periodontal disease each present our patients with a similar magnitude of increased risk for preterm delivery: a two- to threefold increased risk.

Unfortunately, hopes that identifying and treating the conditions could reduce risk and improve pregnancy outcomes have been dashed – in both cases. In the case of periodontal disease, three major randomized controlled trials in the United States – including the Periodontal Infections and Prematurity Study (PIPS) published in February of this year – have provided evidence that screening and treating periodontal disease during pregnancy are not likely to reduce rates of preterm birth.

This does not mean, however, that we should ignore the problem of periodontal disease. It is a huge problem, affecting up to 40% of pregnant women according to most reports and there is no evidence to suggest that dental examinations or treatment are deleterious during pregnancy. In all the studies that have been done over the last decade or so, there is nothing to suggest that we shouldn’t look for periodontal disease and treat it.

Periodontal disease is clearly associated with other poor health outcomes, in addition to its association with preterm birth, and study after study has shown that good oral health is important for good overall health.

Despite our inability to reduce preterm birth rates with periodontal treatment, it is important to recognize the value of good oral health for all adults, including pregnant women.

The Disease and Its Effects

Periodontal disease often evolves from untreated gingivitis, which causes the gums to redden, swell, and bleed more easily. Bacterial plaque on the surface of the teeth spreads and grows below the gum line (dentistry speaks of a subgingival biofilm), adding to progressive gram-negative anaerobic infection of the mouth and inflammatory responses that ultimately lead to the destruction of tissue and bone.

As Dr. Kim A. Boggess has described in numerous articles on periodontal disease in pregnancy, damage occurs both directly from bacteria in plaque and indirectly through bacterial stimulation of local and systemic inflammatory and immune responses.

Interestingly, there is no single validated definition of periodontal disease. Instead, the clinical criteria used to define periodontal disease have varied among studies, which can make all the data difficult to interpret. Some investigators have focused on the magnitude and extent of attachment loss or other clinical measures of periodontal disease, whereas others have gone in on measures of infection and host response to oral bacteria. There are commonly agreed upon clinical markers, however, including gingival recession, tooth attachment loss, and bleeding on gingival probing.

Much of the research into the role of oral health in pregnancy outcomes has been driven by appreciation of the importance that oral health plays in overall general health, and by a growing recognition that periodontal disease can trigger chronic, systemic inflammation, which in turn can drive various disease processes.

The conditions most often associated with periodontal disease are cardiovascular disease and diabetes. Some studies published in the last decade have shown, for instance, that individuals with periodontal disease have at least a 1.5-fold increased risk of developing cardiovascular disease. There also is some evidence that treating periodontal disease can improve various measures of cardiovascular function – such as blood pressure and levels of inflammatory cytokines. In addition, some data suggest that periodontal treatment results in better diabetic control.

Maternal periodontal disease also has been associated with other adverse pregnancy outcomes such as preeclampsia, gestational diabetes, fetal loss, and low birth weight. In a “clinical expert series” on maternal oral health in pregnancy published in 2008, Dr. Boggess provides a comprehensive summary of the literature on these associations, and details why good oral health should be a goal for all individuals, including pregnant women (Obstet. Gynecol. 2008;111:976-86).

Treatment and Preterm Birth

While some of the initial studies of periodontal treatment in pregnancy were promising, suggesting that treatment may reduce the risk for preterm birth, we now have three large studies in the United States that have been negative. Each has involved randomization to active treatment with scaling and root planing or placebo treatment, and each has shown no significant difference in preterm birth between the two groups.

In the most recent Periodontal Infections and Prematurity Study (PIPS) trial reported early this year, we screened more than 5,500 women between 6 and 20 weeks’ gestation and found a prevalence of periodontal disease of 50%. We defined periodontal disease as attachment loss of at least 3 mm on at least three teeth. Moderate to severe disease was defined as attachment loss of 5 mm or more on three or more teeth.) The 756 women with periodontal disease who returned for the scheduled treatment visits were then randomly assigned in a 1:1 ratio to active treatment or placebo (superficial cleaning). The mean gestational age at screening was 13.1 weeks, and the mean gestational age at treatment was 16.5 weeks. The groups were balanced with respect to gestational age, periodontal disease severity, and history of preterm delivery (Am. J. Obstet. Gynecol. 2010;202:147.e1-8).

There was no significant difference between the two treatment groups in the incidence of spontaneous preterm birth at least 35 weeks’ gestation (our primary end point) or at less than 37 weeks’ gestation. We also saw no difference in...
mean birth weight or the proportion of low-birth-weight or very-low-birth-weight newborns. There was also no difference in composite neonatal mor-
bidity/mortality between the groups.

These findings are largely concordant with those of two other recent studies. In one study published in 2006, more than 800 women were randomly assigned to receive either antepartum periodontal treatment (before 21 weeks’ gestation) or postpartum treatment (control). Periodontal treatment improved measures of periodontitis but did not significantly alter the risk of preterm delivery at less than 37 weeks gestation (N. Engl. J. Med. 2006;355: 1885-94).

The other study – coined the MOTOR study (Maternal Oral Therapy to Reduce Obstetric Risk) – randomized more than 1,800 patients at three sites to periodon-
tal treatment early in the second trimester or delayed treatment after delivery. Again, investigators demonstra-
ted improvements in oral health after treatment, but found no significant re-

Current Thinking
What should we do in the wake of these negative findings?

First, we must realize that periodontal treatment in these trials improved the oral health of pregnant women, and that the patients in these studies might be different from those in our study. Second, we must still appreciate – and share with our patients – that peri-
dontal disease is very common and does appear to be associated with preterm
birth (and possibly other adverse pregn-
ancy outcomes), as well as with other negative health outcomes such as cardio-
vascular disease and diabetes.

Therefore, we can be careful, nuanced, and be sure to tell patients that treatment of periodontal disease alone does not ap-
pear to reduce the risk of preterm birth.

We need to study these associations further and better understand the mech-
anisms of periodontal disease–associat-
ed preterm birth. There also are unan-
swered questions about treatment. For example, is it possible that treatment prior to pregnancy may reduce the risk of preterm birth? Is it possible that using adjuvant antibiotic mouthwash may improve pregnancy outcomes? Quest-
ions such as these should be answered with additional clinical trials.

We also must better understand and delineate reported disparities in oral
health. Periodontal disease disproport-
nionately affects racial and ethnic minorities and those of low socioeco-
nomic status. While differences in access to care and other behavior and practices likely play a role in these disparities, ex-
pertise believe that there also may be pop-
ulation differences in oral microbiology or inflammatory responses to bacterial colonization.

As we wait for more information, we can tell our patients about the impor-
tance of good oral health, and we can reassure them that periodontal disease treatment in pregnancy appears to be safe. We are not ready, however, to rec-
ommend routine screening and treat-
ment of periodontal disease in paren-
ancy to improve pregnancy outcomes.

Dr. Macones said he has no disclosures relevant to this article. E-mail him at obnews@elsevier.com.