MASTER CLASS

Infection's Relationship to Prematurity

E. ALBERT REECE, M.D., PH.D., M.B.A.

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 asynchrony between its investments and such an adverse 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 rates. The studies so far have been controversial, leaving obstetricians very confused as to how they can best intervene and improve the perinatal outcome.

It is because of this very difficult situation that we believe it is important to have a Master Class that examines 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. REECE, *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.*

Periodontal Disease and the Risk of Preterm Birth

During the last 10-15 years, in an effort to improve troubling 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.

GEORGE A. MACONES, M.D.

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 hone 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 maternal 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 multicenter Periodontal Infections and Prematurity Study (PIPS) trial reported early this year, we screened more than 3,500 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 visit 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 less than 35 weeks' gestation (our primary end point) or at less than 37 weeks' gestation. We also saw no difference in

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mean birth weight or the proportion of low-birth-weight or very-low-birth-weight newborns. There also was no difference in composite neonatal morbidity/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 periodontal treatment early in the second trimester or delayed treatment after delivery. Again, investigators demonstrated improvements in oral health after treatment, but found no significant reduction in preterm birth at less than 37 weeks of gestation (Obstet. Gynecol. 2009;114:551-9).

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 benefits of good oral health cannot be disputed. Secondly, we must still appreciate – and share with our patients – that periodontal disease is very common and does appear to be associated with preterm birth (and possibly other adverse pregnancy outcomes), as well as with other negative health outcomes such as cardiovascular disease and diabetes.

We should be careful, however, and be sure to tell patients that treatment of periodontal disease alone does not appear to reduce the risk of preterm birth.

We need to study these associations further and better understand the mechanisms of periodontal disease–associated preterm birth. There also are unanswered 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? Questions such as these should be answered with additional clinical trials.

We also must better understand and delineate reported disparities in oral health. Periodontal disease disproportionately affects racial and ethnic minorities and those of low socioeconomic status. While differences in access to care and other behaviors and practices likely play a role in these disparities, experts believe that there also may be population differences in oral microbiology or inflammatory responses to bacterial colonization.

As we wait for more information, we can tell our patients about the importance 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 recommend routine screening and treatment of periodontal disease in pregnancy to improve pregnancy outcomes.

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

Select Criteria Denote High-Risk SLE Pregnancies

BY M. ALEXANDER OTTO

FROM THE INTERNATIONAL CONGRESS ON SYSTEMIC LUPUS ERYTHEMATOSUS

VANCOUVER, B.C. – Monthly monitoring by rheumatologists of every pregnancy in every woman with systemic lupus erythematosus may be unnecessary, according to Dr. Michelle Petri.

A relatively small list of criteria can distinguish high-risk pregnancies in women with systemic lupus erythematosus (SLE) – ones that carry a higher likelihood of miscarriage, extreme prematurity, and SLE flare – from others, and signal the need for intensive monitoring by obstetricians and rheumatologists, Dr. Petri said at the meeting.

At present, however, there is little effort to make such distinctions, so most SLE pregnancies are subjected to monthly visits to rheumatologists and obstetricians, and, starting at week 26, weekly monitoring by obstetricians.

That's not always necessary; women are subjected to needless anxiety and hospital resources are wasted, Dr. Petri said.

Based on the Hopkins Lupus Cohort, a database that has been tracking several thousand patients with SLE over the past 25 years, Dr. Petri and her colleague, Duke University rheumatologist Dr. Megan Clowse, have identified those factors that truly put women and fetuses at risk during SLE pregnancies.

Pregnancy and the postpartum period are hard on the kidneys of women with SLE, though organ involvement elsewhere in the body tends to lessen, said Dr. Petri, professor of rheumatology at Johns Hopkins University, Baltimore.

"Proteinuria from active lupus significantly increases, and this continues even after delivery," she added.

Therefore, pregnant women with lupus nephritis truly do need close monitoring. Dr. Petri recommended monthly urine protein-creatinine ratios to detect a worsening of the condition and the need for treatment.

She noted that the ranges on urine dipsticks are too broad; the dipstick is not adequate as a monitoring tool for nephritis.

In terms of fetal health, the risk of miscarriage doubles if, at the first pregnancy visit, a woman is proteinuric, thrombocytopenic, or hypertensive, or has a history of antiphospholipid syndrome.

The risk triples if two or more of these conditions are present, Dr. Petri said. The presence of antithyroid antibodies also increases the risk of miscarriage.

In addition, active SLE, especially if accompanied by anti–double-stranded DNA antibody or low complement levels, predicts extreme prematurity. Autoimmune thyroid disease also appears to be associated with preterm birth.

Screening for the various factors, "we can predict at the first pregnancy visit if there's going to be a poor outcome," Dr. Petri said.

If the risk factors are present, monthly monitoring by a high-risk obstetrician, followed by weekly monitoring at week 26, are appropriate to gauge if, and when, a rescue delivery is needed.

Otherwise, and absent renal involvement in the pregnant patient, SLE pregnancies may not need to be classified as high risk, Dr. Petri said.

"Since we can stratify women at risk for miscarriage and extreme prematurity, and know the only organ we have to worry about is the kidney, we can come closer to using our resources appropriately," Dr. Petri said.

To reassure women, rheumatologists should "get the word out to patients that high-risk interventions are not necessary for every [SLE pregnancy]," she said.

Dr. Petri said she had no disclosures to report. ■

Ketamine Reduces Post C-Section Pain at 6 Weeks

BY MIRIAM E. TUCKER

FROM THE ANNUAL MEETING OF THE SOCIETY FOR OBSTETRIC ANESTHESIA AND PERINATOLOGY

SAN ANTONIO – A single postpartum low dose of ketamine significantly and persistently reduced pain for up to 6 weeks after cesarean delivery compared with placebo, but there were no significant differences in chronic pain or depression between the two groups at 1 year, in a randomized, double-blind study of 82 women.

VITALS

Major Finding: Patients in the ketamine group reported significantly less pain at 6 weeks post partum, with scores of 1.3 vs. 2.3, but there were no significant differences at 6 weeks in depression or at 1 year in pain or depression.

Data Source: One-year follow-up of 82 parturients from an initial randomized, controlled trial of 188.

Disclosures: None was reported.

Low doses of the *N*-methyl-D-aspartate (NMDA) antagonist ketamine have been shown to decrease postoperative opioid requirements, and the drug has also been shown to have an antidepressive effect (Arch. Gen. Psychiatry 2006;63:856-64). Those data led to the hypothesis that women who receive a single intravenous dose of ketamine might be less likely to develop postpartum depression or chronic pelvic pain, said Dr. Laurie Chalifoux of Northwestern University, Chicago.

A total of 188 women were randomized to receive either 10 mg IV ketamine or saline by a blinded anesthesiologist 5 minutes after cesarean delivery.

All received scheduled IV ketorolac 30 mg every 6 hours for 24 hours, along with 1 or 2 tablets of acetaminophen 325 mg/hydrocodone 10 mg every 4 hours as needed for breakthrough pain.

Among those 188 women, the group who received ketamine reported significantly lower numeric pain rating scores (on a scale of 1-10) than did those receiving saline.

However, there were no differences at any other time point, Dr. Chalifoux reported at the meeting.

The 82 patients who were available for an interview 1 year later were asked to report pain scores (1-10) and whether they had a self-diagnosis of depression at both 6 weeks and 1 year post partum. Patients in the ketamine group reported significantly less pain at 6 weeks post partum, with scores of 1.3 vs. 2.3.

Depression did not differ at 6 weeks, with just one woman (2%) from each group reporting that she was depressed at that point.

At 1 year, pain scores were nearly 0 in both groups and did not differ significantly (0.1 with ketamine vs. 0.0 with saline).

Depression also did not differ significantly, although there were two women (5%) who reported being depressed at 1 year in the saline group compared with none in the ketamine group.

It's possible that a higher dose than 10 mg might have had a greater impact, given that the previous studies showing analgesic and antidepressive effects used doses ranging from 0.15 to 1.0 mg/kg. However, the potential side effects of ketamine – including dysphoria, memory loss, hallucinations, seizures, nystagmus, hypertension, tachycardia, and nausea/vomiting – suggest that dosages should be kept in the lower ranges, Dr. Chalifoux noted.

Also, it's possible that ketamine might not have a large impact among healthy parturients, but it might among those who are at increased risk for depression or chronic pain, she said. ■